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The Clinical Aspects of ARTERIOSCLEROSIS



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To my wife,
RITA
and our children
LOIS AND ROBERT
the trio
who so fully understand
the way of life of a
physician and his family

Foreword

THE GREAT problems of medicine are functions of time, place and economic development. In primitive societies, the major challenges derive from the noxious effects of undernutrition and the infective and traumatic hazards of the environment. These causes of morbidity and mortality recede pari passu with advancing culture. The result is that a higher proportion of the population reaches the time of life in which the endogenous processes of physical deterioration inherent in all living substance attain significant intensity. Economic advance, at least in contemporary Occidental Civilization, most often brings in its wake a diet containing more animal lipids. From the evidence available at present, it appears likely that this combination of an aging population and a diet rich in animal lipid has created a milieu favorable to the development of atherosclerosis But whether or not this pathogenesis is factual, there can be no doubt of the enormous increase in the frequency of atherosclerosis in the Western World In the thirty-five years that the writer has practiced medicine in New York City, an infinitesimal moment in medical evolution, the augmented incidence of coronary thrombosis and other atherosclerotic diseases has been all too evident; it has not been a matter of improved diagnosis, for my teachers of three decades ago were well acquainted with the clinical manifestations of coronary disease and certainly with its post mortem recognition. There is no doubt that in the Western World atherosclerosis has succeeded to the grisly title of *Captain of the Men of Death* held in the past by such redoubtable scourges as starvation, war, tuberculosis, malaria, bubonic plague and pneumonia Moreover, the greater case incidence of arteriosclerotic disease does not fully measure the increment in the proportion of the contemporary physician's effort which is devoted to the victims of arteriosclerosis. For the introduction of intensive sodium restriction and mercurial diuretics has greatly prolonged the average duration of life in coronary disease and the antibiotics have done the same for sufferers from cardiac, cerebral and other localizations of arteriosclerosis. Diabetic and hypertensive patients live longer than before, and the late stages of both diseases are dominated by the consequences of arteriosclerosis The result is that a startling proportion of the patients in the medical, neurological and psychiatric wards are there because of arteriosclerotic disease.

The enormity of the challenge presented by the arteriosclerotic maladies has of course called forth a corresponding increase in clinical and experimental investigation The resulting literature is gargantuan and scattered

throughout the journals of every branch of medicine as well as in numerous monographs dealing primarily with experimental investigation, pathological anatomy or the clinical aspects of arteriosclerotic disease of the heart, brain, extremities or other individual organs. But the practitioner must deal every day with arteriosclerotic disease in various organs. It is hardly feasible for him to keep abreast of this vast scattered literature, or for the specialist to follow the publications in fields other than his own Dr. Rinzler's book integrates in a single volume the totality of the clinical aspects of arteriosclerosis in coordination with recent basic investigations along morphological, physiological, biochemical, geopathological, and epidemiologic lines. He has surveyed the enormous literature and subjected it to critical analysis in the light of his own extensive studies and experience. The pathogenesis of arteriosclerosis is still very much sub judice, but in the forty odd years since Anitschkow first rendered rabbits atheromatous by feeding cholesterol, a great deal has been achieved by investigation along diverse paths, and this is judiciously evaluated by Dr. Rinzler. He presents the evidence which negates the formerly dominant nihilistic view that atherosclerosis is an almost inevitable concomitant of senescence and shows that it is a potentially reversible process The major objective of Dr. Rinzler's book, however, is the elucidation of the clinical aspects of arteriosclerosis, and in this he has succeeded in superlative fashion. Diagnosis, prognosis and treatment of the arteriosclerotic diseases are all covered in the light of both an exhaustive survey of the world literature and his own experience and work. Especially noteworthy and detailed are the sections on arteriosclerotic heart disease, quantitatively the most important of the arteriosclerotic diseases, which Dr. Rinzler has studied intensively for many years and to the understanding of which he has substantially contributed. The discussion of cerebral arteriosclerosis is illuminated by the addition of the point of view of the internist to this primarily neurologic subject

The profession is indebted to Dr. Rinzler for undertaking and successfully accomplishing the tremendous task of elucidating present-day knowledge of arteriosclerosis and its consequences In his book, medical student and practitioner will find a comprehensive, authoritative and judiciously evaluated presentation of which is known of the nature, clinic and treatment of the arteriosclerotic diseases

ARTHUR M. FISHBERG, M.D

New York, New York

Preface

THE UPSURGE in interest in arteriosclerosis over the past decade from the experimental and therapeutic viewpoint, plus the reported increase in incidence of arteriosclerosis because of the longer life span, prompted this book which deals with a holistic approach to the clinical problems in arteriosclerosis. I have stressed the arteriosclerotic patient as seen by the general practitioner, in particular, by emphasizing the diagnosis and therapy of the major and minor manifestations of arteriosclerosis from head to foot. However, the specialist, especially in the medical branches, may find the text of general interest.

The greater part of the book has been devoted to the cardiac, cerebral and peripheral vascular manifestations of arteriosclerosis, and, rightfully so, since these organs are most commonly involved in this disease and account for the highest incidence of morbidity and mortality. The chapter on General Considerations represents an attempt to orient the reader in the present-day direction of thought with regard to the etiology, to the abnormalities in the biochemical processes, and to the co-related diseases.

Acknowledgments, as alluded to in the inscriptions, are due to many of my colleagues My original interest in the clinical aspects of arteriosclerosis began in 1941 when, under the aegis of Dr. Harry Gold, I was permitted to attend the meetings of a Committee of the New York Heart Association which was planning the study of the life history of arteriosclerosis. Dr. Janet Travell and I also began at this time a collaboration, both at Dr. Gold's Cardiac Clinic at Beth Israel Hospital and at the Department of Pharmacology at Cornell University Medical College, of studies on cardiac pain and on coronary dilator drugs which led to the publication of a monograph on Cardiac Pain in 1951. Dr. Travell, Dr Gold and Dr McKeen Cattell, Professor of Pharmacology at Cornell University Medical College, have shown interest, kindness and have been of utmost help beyond the call of duty in the pursuit of my studies The Cornell Conferences on Therapy, conducted by the Department of Pharmacology, have been a great source of instruction in therapeutic matters.

Dr. Arthur Fishberg, Director of Medicine at Beth Israel Hospital, was kind enough to review the text in the early stages of its writing His ward service rounds and teachings have contributed greatly to my understanding of the in-patient problems in arteriosclerosis Dr Abraham Schlossman critically reviewed the section on retinal aspects of arteriosclerosis Dr. Abraham Geffen, of the Department of Radiology at Beth Israel Hospital, kindly supplied some of the roentgen films used in this book. For several years after

1946. Dr. Seymour Rogers was the surgical half of the team in the Peripheral Vascular Clinic at Beth Israel Hospital, and we worked together until Dr. Rogers left New York.

I am grateful to Dr. Howard A. Rusk, Director of the Department of Physical Medicine and Rehabilitation at Bellevue Hospital, for permitting the studies of drug therapy in the treatment of hemiplegia and of the rehabilitation of the cardiac, and for the opportunity to observe, on his service, the cerebro-vascular and spinovascular complications of arteriosclerosis. Dr. Arthur C. Corcoran, of the Cleveland Clinic, was most helpful with suggestions for improving the text just before it went to press. The arduous task of proofreading the text was assumed by my wife, Rita. For this and much more, I give her my heartfelt thanks.

It is with great appreciation that I would like to acknowledge the grants from The National Heart Institute of the United States Public Health Service, The Josiah Macy, Jr., Foundation and the Loyal League Philanthropies, which directly or indirectly made possible our clinical studies.

My secretaries through the years of the writing of the text have been Corinne Futterman, Linda Dubester, Irene Friedman and Myrna Cassin.

SEYMOUR H. RINZLER, M.D.

New York City

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The Clinical Aspects of
ARTERIOSCLEROSIS

No man is an Iland, intire of itselfe.

JOHN DONNE

I live not in myself, but I become
Portion of that around me

BYRON

I am a part of all that I have met

TENNYSON

Chapter I

General Considerations

The CLINICAL problems in vascular disease due to arteriosclerosis arise from occlusive intimal disease (atherosclerosis) (1) of the small and medium-sized arteries (2) and statistically affect mainly the heart, brain and lower extremities (3). However, a "head to foot" approach to the problem of the patient with arteriosclerosis must be made since arterial insufficiency or occlusion may, under suitable circumstances, be found in any artery (4-6). It is the purpose of this volume to deal with the clinical aspects of arteriosclerosis primarily from the points of view of diagnosis and therapy.

DEFINITION OF ARTERIOSCLEROSIS

Moschcowitz (7) defines arteriosclerosis as a progressive and irreversible affection of the arteries in which hyperplasia of one or more of the structural elements is a primary reaction, with deposition of lipids, collagenous tissue, hyalin and calcium as a secondary reaction, the totality of both components resulting in thickening, dilatation, deformity, and loss of elasticity of the walls Arteriosclerosis is to be regarded as a generic term (8) which includes such entities as atherosclerosis, Monckeberg's sclerosis, atheromatosis and hyperplastic arteriosclerosis Atheromatosis (9) indicates a degenerative lesion in which lipid material, particularly cholesterol, is accumulated in the intima. This is a reversible condition. Atherosclerosis indicates the presence not only of lipid material and often calcium, but also of reactive connective tissue proliferation. Here the primary target is the intima and the goal, complete occlusion of the arterial lumen True Monckeberg's sclerosis is associated with calcification of the medial coat and not necessarily with lesions of the intima. Hyperplastic arteriosclerosis (10, 11) refers to the normal involutionary process which arteries undergo from birth to maturity. Arteriosclerosis is to be regarded as an exaggerated phase dependent on such factors as intravascular pressure, normal and increased, the composition of the blood, perivascular stresses and fixations, the vascular supply of the blood vessel walls and tissue permeability.

THE INCIDENCE OF ARTERIOSCLEROSIS

Arteriosclerosis is found in 25 per cent of people between 40 and 49 years, 48 per cent of people between 50 and 59 years, 78 per cent of people between 60 and 69 years, and 90 per cent of people over 70 years of age. In 1951 (12) the total deaths from all causes in the United States were

1,481,000. Cardiovascular diseases accounted for 767,000 (51.8 per cent) of these deaths. Arteriosclerotic heart disease, including coronary disease, caused 338,000 (44.1 per cent) deaths. General arteriosclerosis resulted in 37,000 (4 8 per cent) deaths. Vascular lesions affecting the central nervous system (mixed hypertension and arteriosclerosis) caused 158,000 (20 6 per cent) deaths In the year 1951, *cardiovascular disease caused over half of all deaths, and arteriosclerosis and hypertension caused over 90 per cent of all deaths from cardiovascular disease.*

Statistics gathered by the New York Heart Association in 1952 indicated that 500,000 of the 8,000,000 population of New York City were suffering from diseases of the heart and circulation Of a total of 81,239 deaths,

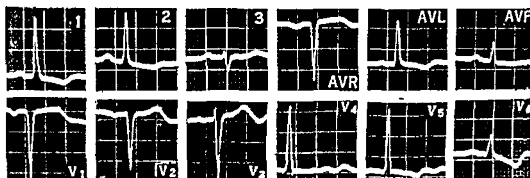


Fig. 1. Electrocardiogram of a 59-year-old white male with arteriosclerotic heart disease taken ı
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42,729 were due to disease of the heart and circulation, with diseases of the heart resulting in 35,684 deaths and vascular lesions of the central nervous system causing 5,560 deaths The number of attacks of coronary occlusion that occur annually has been estimated to be between 500,000 (13) and 1,000,000 (14, 15). Gould (9) estimated that in 1953 there were approximately 600,000 persons living in the United States who had had one or more myocardial infarctions

The co-occurrence of arteriosclerosis in various parts of the body. Patients under 40 years of age: Berlin (16) found no evidence of clinical coronary artery disease in 11 cases of cerebral thrombosis in young adults One patient examined at autopsy showed no disease of the coronary arteries.

Gertler (17) in discussing myocardial infarction in patients under 40 years of age, does not mention any clinical atherosclerosis elsewhere in the body. Yater (18) presented autopsy data on 450 patients of from 18 to 39 years of age who died of coronary thrombosis Clinical evidences of cerebral or peripheral vascular disease were absent. Cerebral arteriosclerosis

at autopsy was present in a mild to moderate degree in 10 patients. Arteriosclerosis of the kidneys were found in 6 patients. In a few patients in whom there was considerable atherosclerosis of the aorta, the first portion of the intercostal arteries, lumbar arteries, celiac artery, mesenteric artery or renal arteries was also involved In 191 patients there was atherosclerosis of the aorta, but in 103 the lesions were comparatively insignificant. Yater concluded that coronary artery sclerosis in this series was a specific disease in the coronary arteries and was not a part of generalized arteriosclerosis.

It would seem that in those under 40 years of age, the clinical manifestations of atherosclerosis appear in a single organ. This is to be contrasted

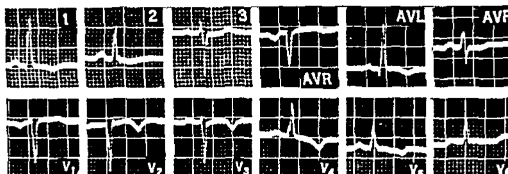


Fig. 2. Electrocardiogram of a 58-year-old white female illustrating a previous anterior wall infarction, Q_1T_1 pattern

with the clinical finding of simultaneous atherosclerosis in various parts of the body in the older age groups

The co-occurrence of arteriosclerosis in various parts of the body. Patients over 40 years of age: Boas and Epstein (19) studied the prevalence of manifest atherosclerosis of a working union population of 32,000 male and female garment workers over 40 years of age by examination of 343 men and 225 women who represented a sample of this total union population The average age of the men was 60 years, and of the women, 54 years

Their method of examination for the presence of atherosclerosis is presented in detail as an example of the techniques useful in the diagnosis of atherosclerosis:

> Each examination includes the following family and medical history, dietary history, complete physical examination, 12-lead electrocardiogram, postero-anterior chest roentgenograms and lateral roentgenograms of the abdomen for evidence of aortic calcifications, blood tests (glucose, cholesterol, phospholipid, uric acid, serological test for syphilis), and urine examination
>
> The diagnosis of atherosclerosis is made whenever evidence of coronary, peripheral, or cerebral artery disease or aortic calcifications, alone or in combination, are found

The diagnosis of coronary disease is based on a definite history of angina pectoris or myocardial infarction or on the following characteristic electrocardiographic signs: Q_1T_1 patterns, Q_3T_3 patterns with concomitant changes in Lead aVf, abnormal Q waves (Q being 20% or more of QRS in Leads I and/or II, 30% or more of QRS in Leads V_5 and/or V_6, or 60% or more in Lead aVf), widening of the QRS interval to 0.12 second or more in the absence of undue cardiac hypertrophy, or S-T elevations or depressions of

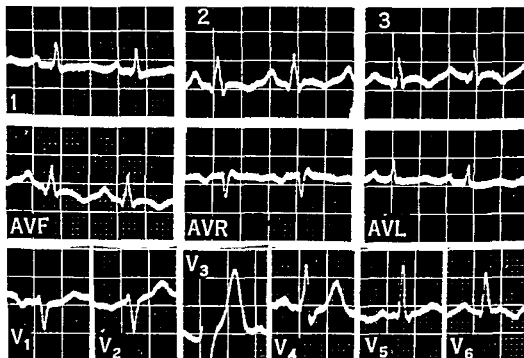


Fig. 3 Electrocardiogram of a 53-year-old white male illustrating a previous posterior wall infarction, Q_3T_3 pattern

2 mm or more in one or more leads, unaccounted for by left ventricular strain, digitalis, or transient causes [Figs. 1-5].

Peripheral artery disease is diagnosed when two or more pulses in one leg or one or more pulses in each leg are absent in the femoral, popliteal, anterior, or posterior tibial arteries *No importance is attached to absent pulsations* in the dorsalis pedis arteries. It is agreed that the absence of pulsations in the major arteries is the most reliable single sign of occlusive arterial disease in the legs. It is occasionally difficult to be certain whether a given pulsation is present, diminished, or absent In such cases, postural color changes and, despite their limited value, oscillometric readings have been used as additional guides Symptoms of intermittent claudication, without objective signs of arterial insufficiency, are not considered diagnostic of peripheral artery disease, since true occlusive disease rarely if ever occurs unless there is absence or diminution of peripheral pulsations.

Cerebral atherosclerosis is diagnosed from a history of a major stroke or an attack of sudden transient dizziness, aphasia, or mental confusion, accompanied by unilateral palsy, or signs of residual lesions of the central nervous system.

Aortic calcifications are diagnosed from postero-anterior 6-ft. (1.8 meter) chest plates and lateral views of the abdomen [Figs. 6 and 7]. The chest films are slightly overpenetrated in order to reveal calcifications more clearly; on an average, 66 kv., 300 ma, with an exposure of 1/10 second is used. Lateral roentgenograms of the abdomen are taken with a Bucky grid at a distance of 36 in. (90 cm.), using 100 ma., and exposure of 2 seconds, and an average of 85 kv., depending on size of the patient. Calcification of the thoracic aorta is diagnosed if definite crescentric shadows are seen in the

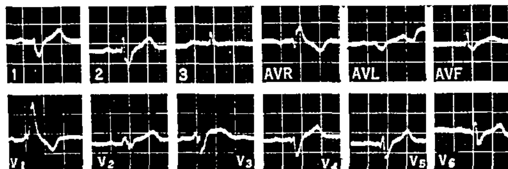


Fig. 4 Electrocardiogram of a 49-year-old white male illustrating a right bundle branch block

aortic knob. Calcification of the abdominal aorta is diagnosed in the presence of single linear densities at least 1 cm long or multiple streaks, in line or parallel, in the proper location Advanced calcification that outlines the aorta is easily recognized

Using these standards, 33 per cent of the men and 23 per cent of the women had one or more lesions of atherosclerosis in various parts of the body. Ten per cent of the men and 2 per cent of the women had evidence of coronary disease; the corresponding figures for peripheral artery disease were 4 per cent in men and 1 per cent in women; those for cerebrovascular disease were 0.6 per cent in men and 0.4 per cent in women As many as 26 per cent of the men and 23 per cent of the women demonstrated aortic calcification on the roentgen film In the men 19 per cent of the calcifications were in the thoracic aorta, 62 per cent were in the abdominal aorta, and 19 per cent were in both sites For women the corresponding figures were 14 per cent, 67 per cent and 19 per cent

Eighteen of the 35 men with coronary artery disease had this as the sole atherosclerotic lesion. Four of 9 with peripheral atherosclerosis had this alone, and 71 of a total of 89 men with aortic atherosclerosis had it as the

sole atherosclerotic lesion. The corresponding figures for women are as follows. 1 out of 5 with coronary artery disease and 46 out of 51 with aortic atherosclerosis.

The co-occurrence of coronary artery disease and peripheral occlusive arterial disease. McDonald (20) studied the incidence of simultaneous occurrence of angina pectoris and intermittent claudication, or the underlying occlusive arterial disease capable of producing either. One hundred thirty-seven patients were studied. Eighty-seven were patients with intermittent claudication due solely to occlusive arterial disease. Fifty other patients had angina pectoris, either on effort or after cardiac infarction. Of 79 patients presenting with intermittent claudication (74 men; 5 women), 23 (29 per cent) had angina pectoris in addition. In 13 the onset of inter-

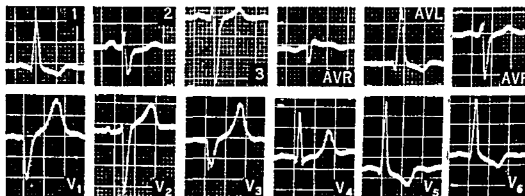


Fig 5. Electrocardiogram demonstrating left bundle branch block in an 80-year-old white male with arteriosclerotic heart disease

mittent claudication preceded that of the angina pectoris, in 6 the angina developed earlier, and in the remaining four symptoms developed at the same time The resting electrocardiograms were found normal in 48 of the 79 patients In 8 (14 per cent) of 56 patients with intermittent claudication who denied angina pectoris, there was electrocardiographic evidence of ischemic heart disease

A diagnosis of ischemic heart disease was made either subjectively (29 per cent) or objectively alone (10 per cent) in 31 of 79 patients who presented with intermittent claudication, a total of 39 per cent Of 50 patients presenting with angina pectoris, 4 (8 per cent) suffered from intermittent claudication and 8 (17 per cent) of the remaining 46 patients without intermittent claudication showed objective evidence of occlusive arterial disease of the legs. Thus, a diagnosis of occlusive arterial disease affecting the legs was made subjectively or objectively in 12 or 24 per cent of the 50 patients (44 men, 6 women) presenting with angina pectoris

Applebaum (284) reported on 888 cases of myocardial infarction in

whom a past history of cerebral or peripheral arteriosclerosis was noted in 26 cases, 10 of the former (1.1 per cent) and 16 (1.8 per cent) of the latter.

The co-occurrence of arteriosclerotic lesions. Pathologic correlation: As for pathologic association, Race and Lisa (21) found that 15 per cent of 100 autopsied cases of myocardial infarction had lesions of cerebral vessels. For the most part in those with central nervous system lesions, the cardiac

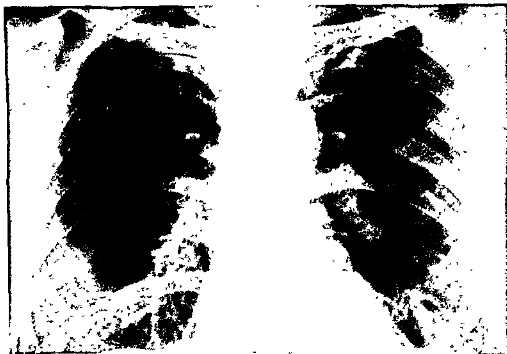


Fig 6. Roentgenogram of the chest of a 73-year-old white male showing calcification of the aortic knob (Courtesy X-ray Department, Beth Israel Hospital, New York)

disease had not been diagnosed. Hicks and Block (22) studied 155 patients who died from apoplexy (hemorrhage, 118, infarction with thrombosis, 12, infarction without thrombosis, 11, ruptured aneurysm, 14). The 12 patients who died of infarction with thrombosis had associated coronary arteriosclerosis in 10 instances, the 11 patients without thrombosis, in 9 instances Ninety per cent of the entire group had hypertension and marked arteriosclerosis was rare The authors attribute the apoplexy to intrinsic functional vascular disease of the brain and the hemorrhages to arterial spasm which produced anoxic damage to the vulnerable deep vessels with diapedesis and coalescence of the hemorrhages

Alpers, Forster and Herbut (23) studied the histology of the retinal and cerebral vessels in 100 adults from blocks taken from the eye (with choroid and retina), the basilar artery, the cerebral cortex including the lepto-

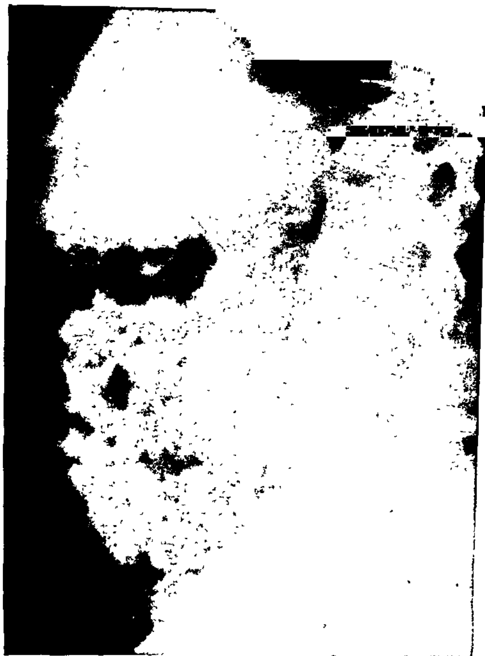


Fig. 7 Lateral roentgenogram of the abdomen of a 73-year-old white male showing calcification of the abdominal aorta. (Courtesy X-ray Department, Beth Israel Hospital, New York City.)

meninges, the globus pallidus, putamen and internal capsule The following arteries in the general systemic circulation were also studied histologically: The aorta; the coronary arteries; the parenchymal arteries of the lungs, adrenal glands; pancreas; spleen and liver; the renal arteries, the larger arteries of the renal parenchyma, and the glomerular arteries. Fourteen pa-

tients had no cerebral or retinal arteriosclerosis. Results of the comparison in the remaining revealed that retinal arteriosclerosis occurs in combination with cerebral arteriosclerosis about six times as frequently as it occurs without cerebral arteriosclerosis. Sclerosis of the cerebral vessels, however, occurs as frequently in the absence, as in the presence, of retinal arteriosclerosis. The distribution of cerebral arteriosclerosis showed that retinal arteriosclerosis indicates a 4:1 possibility that the basilar artery is sclerosed but gives no definite indication that the arteries of the cortex, basal ganglia or meninges are involved. However, the basilar artery and the arteries of

TABLE I

Comparison of Incidence of Retinal, Cerebral and General Systemic Arteriosclerosis in Different Age Groups

Age Group	*No Cases*	*Cerebral, Systemic Arteriosclerosis Only*	*Retinal, Cerebral, Systemic Arteriosclerosis*	*Retinal and Cerebral Arteriosclerosis*	*Retinal and Systemic Arteriosclerosis*	*Systemic Arteriosclerosis Only*	*Cerebral Arteriosclerosis Only*	*Retinal Arteriosclerosis Only*	*No Arteriosclerosis*
15-24	2	1	1	.	.		.		
25-34	5	.	1	.	1	2	1		
35-44	10	4	4	.		.	1		1
45-54	21	7	6	..	1	5	1	1	
55-64	26	10	6	1	1	5	..	2	1
65-74	28	14	13	..	.		1		.
75-	8	5	3		..			.	
Totals	100	41	34	1	3	12	4	3	2

(After Alpers, B J, Forster, F M, and Herbut, P. A (23).)
Courtesy of Dr Bernard J. Alpers and *Archives of Neurology and Psychiatry*

the cortex were more often sclerosed without than with involvement of the retinal artery.

These findings probably account for the clinical point of view of the ophthalmologist (24-27), namely, that retinal arteriosclerosis is considered evidence of cerebral arteriosclerosis and this despite a respectable percentage of cases with sclerosis only of the retinal or of cerebral vessels (28). In contrast, from the clinical viewpoint of the neurologist, convictions are not so strongly in favor of a correlation between cerebral and retinal arteriosclerosis (29)

As for the correlation between systemic and retinal arteriosclerosis, Alpers, Forster and Herbut (Table 1) found that sclerosis of the retinal vessels occurred more commonly with than without sclerosis of the aorta, coronary arteries and splenic arteries Further, sclerosis of these systemic vessels occurred more commonly in the absence of than in conjunction with retinal arteriosclerosis Indeed, sclerosis of all vessels studied occurred more

frequently without than with retinal arteriosclerosis, except for sclerosis of the glomerular arteries.

THE HERITAGE OF ARTERIOSCLEROSIS

The role of heredity in arteriosclerosis especially with relation to cardiac manifestations has been investigated (30-32) and most of the attention has been given to an inborn error in lipid metabolism (33-42). In 1945, Boas and Adlersberg (39) reported on the relative frequency of hypercholesterolemia, xanthoma tuberosum and tendinosum, corneal arcus, xanthelasma and coronary artery disease. They pointed out that in many members of the families of those with hereditary xanthomatosis, the only manifestation of the disease was a high level of serum cholesterol. These authors were not unaware of reported associations between arteriosclerosis and hypercholesterolemia (43-45), but noted that these latter investigators did not confine their observations to younger individuals, nor did any of them study the incidence of hypercholesterolemia among the members of the patients' families.

Subsequent studies by Adlersberg and Boas (34-37, 46) led them to conclude that hypercholesterolemia in primary xanthomatosis was an inborn error of lipid metabolism which gave rise to a predisposition to atherosclerosis Hypercholesterolemia represented the heterozygous abnormal state while xanthoma represented the homozygous abnormal state. They carefully pointed out (37) that this hereditary disturbance of lipid metabolism was only one conditioning factor for the development of atherosclerosis and that many additional factors were probably involved: anatomic peculiarities, such as coronary intimal thickening in the male (47), variations in permeability of the intima (48) and alterations of the intercellular ground substance.

More specifically (36, 37), when 35 families with xanthoma tuberosum and xanthoma tendinosum, comprising 172 members and an additional 29 persons known to belong to such families (total of 201 persons) were examined for hypercholesterolemia, coronary artery disease and other stigmata of this disorder, the following results were obtained serum cholesterols done by Bloor's method were determined in 175 of the 201 subjects and found elevated above 300 mg. per cent in 57, cardiac symptoms developed before the age of 50 in 49 patients, xanthelasma was found in 61 patients, tuberous or tendinous xanthoma in 25, and corneal arcus in 35.

These results are to be compared with those obtained in 122 patients with proved disease of the coronary arteries, unselected except as to age (under 50 years) Seventy-one (58 per cent) had hypercholesterolemia. In addition, 50 families of these 122 patients were studied In 15 families, all or most siblings exhibited hypercholesterolemia. Many siblings exhibited corneal arcus and xanthelasma; a few showed xanthoma.

An analysis of 500 patients who represented consecutive admissions to a general hospital (48) for signs and symptoms of idiopathic hypercholesterolemia indicated that hereditary hypercholesterolemia occurs in about 5.5 per cent of the population. A further study of idiopathic hypercholesterolemia in 200 randomly selected families in Staten Island, New York, indicated that hypercholesteremia was significantly greater among children of hypercholesteremic parents than it was among children of normocholesteremic parents (49).

With respect to clinical significance of the heritage of arteriosclerosis, the serum cholesterol of all relatively young patients with coronary atherosclerosis should be determined as the initial step in uncovering hypercholesterolemia in members of their immediate family. Those with elevated cholesterol levels should be examined for latent cardiovascular disease and should be kept under permanent medical supervision (36)

Wilkinson, Hand, and Fliegelman (42) studied essential familial hypercholesterolemia in four generations composed of 282 individuals. They concluded that the increase in blood cholesterol was endogenous, not dietary and that the condition is inherited as an "incomplete" dominant trait.

Thomas (32, 50) stated that preliminary genetic analysis indicated that hypertension bears an etiological relationship to coronary artery disease and that the same heritage is expressed more often as hypertension in females and as coronary artery disease in males.

Thomas and Cohen (51) analyzed the prevalence of hypertension, coronary artery disease, obesity and diabetes among the parents, grandparents, aunts and uncles of 266 Johns Hopkins' medical students. A study of the incidence of these disorders in siblings of affected and non-affected parents showed that coronary artery disease was nearly four times as prevalent among siblings of individuals with coronary artery disease as among siblings without it. Hypertension was three times as frequent among siblings of hypertensive individuals as among siblings of normotensive individuals, for obesity, it was four times, for diabetes, eight times.

Page, Lewis and Gilbert (290) found coronary artery disease to be rare among the Navajo Indians, this in spite of diet and living habits not strikingly different from a control group of citizens of the city of Cleveland, Ohio who show a higher incidence of coronary artery disease. Heredity was suggested as the best explanation for the low incidence of coronary disease and the low level of cholesterol among these Indians

THE PATHOLOGY OF ARTERIOSCLEROSIS

The basic pathologic alterations in arteriosclerosis [Figs. 8 to 11] consist of the formation of atheroma, fibrous plaques and the deposit of calcium (52-73). The earliest macroscopic changes occur in the form of yellowish minute spots of lipoid material visible beneath the intima, which are round

and scarcely elevated above the surface (9, 69, 74). These spots become more numerous and the process in general increases in severity with age (75).

Contradictory evidence has been offered in regard to the frequency and degree of intimal thickening in male infants. Dock (47) and Fangman and Hellwick (76) found pathologic evidence of such masculine predominance. Minkowski (61) was unable to show that any sex difference in intimal thickening at birth existed.



Fig. 8 Photomicrograph of section through the wall of a carotid artery demonstrating thickening of the intimal wall. Note position of the internal elastic membrane first near the endothelial surface and then in the middle of the arterial wall (Hematoxylin-eosin.)

Gould (9) places the order of localization with relation to the coronary circulation thusly: First portion of anterior descending branch; main stem of left coronary; first portion of right coronary, and first portion of left circumflex branch Other early lesions include (62): (1) appearance of increased amounts of mucoid ground substance in the intima and media; (2) proliferation of subendothelial fibroblasts, and (3) small areas of degeneration in the internal elastic membrane. Yater (18) lists the following pathologic findings in early atherosclerosis

1. Simple plaque formation, the plaque being composed of moderately loosely arranged connective tissue frequently containing young fibroblasts.
2. Absence of calcium.
3. Presence only occasionally of a small nidus of amorphous material in the plaque.
4. Slight, if any, vascularization of plaque or media.
5. Few, if any, cholesterol crystals in the plaque.
6. Slight to moderate damage to the internal elastic lamina, which usually may be identified
7. Slight thinning with minimal interstitial fibrosis of the media below the plaque.

While atheroma may be seen at the beginning of the second decade or younger (69), fibrous plaques begin to appear during the fourth decade. These are in the form of a hyaline-like connective tissue, joining rounded

or irregular plaques of white color which encroach upon the lumen. These plaques may then become calcified (9). Moderately advanced atherosclerosis has the following characteristics (18):

1. Hyalinized base of the plaque.
2. Presence of a large mass of amorphous cholesterol or lipid in the plaque.
3. Surface of plaque composed of compact fibrous tissue in which a few fibroblasts persist.



Fig 9 Left anterior descending coronary artery, intimal thickening, calcification of the wall and recanalization of the thrombosed vessel. (Hematoxylin-eosin)

4. Minimum calcium deposition in center of plaque, usually in the form of fine calcium granules or calcified nuclei of fibroblasts
5. Presence of a few cholesterol clefts.
6. Slight marginal vascularization.
7. Fragmentation or frequent absence of internal elastic lamina
8. Moderately thin, occasionally vascularized media, with loss of muscle fibers and increased fibrosis below plaque.

The following changes are associated with advanced atherosclerosis (18).

1. Complete or almost complete hyalinization of the plaque, both base and surface zones, with fibroblasts remaining only at the margin
2. Masses of calcium in plaques.
3. Frequent presence of cholesterol clefts
4. Common presence of broad vascular channels at margin and base of plaque.

sclerosis wherever veins are subject to prolonged increase in venous pressure, and particularly arteriosclerosis of the pulmonary artery and its branches caused by such conditions as mitral stenosis and pulmonary diseases leading to cor pulmonale."

Intimal Permeability: It was Virchow's contention that lipids in the intima were deposited there by direct infiltration from the plasma. Modifi-

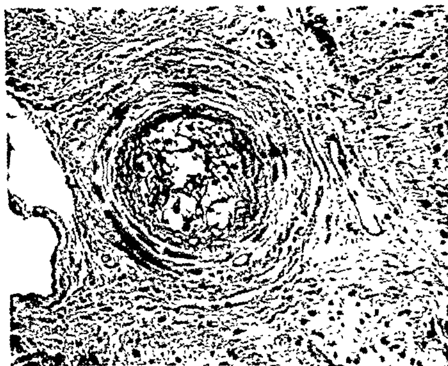


Fig 11. Atherosclerotic lesion of the central retinal artery (x 255) (Courtesy Registry of Ophthalmic Pathology of the Armed Forces Institute of Pathology, Accession No 203245.)

cations of this thesis have been offered. Leary (56, 81, 82) believed that lipid-carrying macrophages are attracted to the intima by a process of chemotaxis, penetrate the endothelium and deposit the lipid material in the intima Winternitz (83) attributed the primary change to hemorrhage from the vaso vasorum or directly from the lumen Hueper's (84, 85) belief is that the initiation of the atheromatous process is a precipitation of a cholesterol film on the intimal surface This first causes a reduction in permeability of the vessel wall and then through anoxic injury to the endothelium secondarily causes an increased permeability which leads to the formation of subintimal lipid atheromas Pollak (64, 86, 87) offers an etiologic concept of atherosclerosis based on a study of intimal alterations after shock. In all persons exposed to shock (infants, children, adults and old

5. Absence of, or severe damage to, internal elastic lamina.
6. Hyalinization or atrophy of media, with loss of muscle and increase in fibrous tissue

THE PATHOGENESIS OF ARTERIOSCLEROSIS

Widely divergent concepts of the pathogenesis of arteriosclerosis still exist (77-80). The broader aspects of etiology include intravascular filtration pressure, permeability of the arterial intima, blood composition (serum lipids) and the removal of lipids from the arterial wall.



Fig 10 Femoral artery demonstrating atherosclerosis and a thrombus lying within the lumen (Hematoxylin-eosin)

Intravascular Filtration Pressure: Moschcowitz (7, 79), has constructed the equation. arteriosclerosis = intravascular pressure × time. He contends that the mere existence of blood pressure is a precursor of atherosclerosis, albeit, other factors being equal: the higher the blood pressure, the earlier the lesion will appear while with normal pressures the longer will be the span of life necessary to produce arteriosclerosis. It is the increased static (lateral) pressure head imposed by gravity, which localizes atherosclerosis in the lower extremities so commonly. As Gubner and Ungerleider (77) point out "further examples may be cited of the role of intravascular pressure in causing atherosclerosis, among them are arteriosclerosis in the aortic arch proximal to coarctation of the aorta, sclerosis of the mitral valve on the ventricular side, sclerosis of the right ventricular endocardium opposite a patent interventricular septum and of the pulmonary artery opposite patent ductus arteriosus, sclerotic changes in the veins opposite the fistulous opening in arteriovenous fistula, phlebo-

of lipoproteins and resorption of most of the foreign material, lipids, namely cholesterol, remain in the subintima where they act as irritants and initiate the alterations which are generally known as atherosclerosis

The relation of coronary atherosclerosis to stress was also pointed out by Enos, Beyer and Holmes (285). In a series of 300 men with an average age of 22 1 years, 77.3 per cent of the cases showed some gross evidence of coronary disease that varied from minimal eccentric thickening to complete

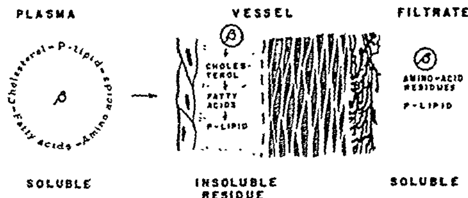


Fig. 13. Schematic representation of passage of lipoproteins through an arterial wall with disruption of the heavily lipid-laden lipoprotein within the wall to give an insoluble residue which provokes tissue reaction (Courtesy of Dr. Irvine H Page and *Circulation* (80).)

occlusion of one or more of the main coronary branches. It was postulated that stress on the intima caused fibroblastic proliferation and the deposition of mucoid ground substance Another factor of importance in the production of the lesions appeared to be the phagocytosis of certain plasma lipids within the traumatized intima

Wang, Schaefer and Adlersberg (88) found that cortisone had a retarding effect on atherogenesis in cholesterol-fed rabbits, despite higher plasma cholesterol levels This effect of cortisone can be prevented by administration of hyaluronidase, which intensifies atherosclerosis and deposition of cholesterol in the liver The authors conclude that beside the lipid substances in the blood that tissue permeability might also play an important role in atherogenesis.

Removal of Lipids From Arterial Wall: Interference with lymphatic and vaso vasorum drainage of the intercellular fluid causes an accumulation of colloids, such as lipids, in the arterial wall and impaired nutrition to the cellular elements of the artery, favoring the development of atherosclerotic and degenerative changes. Phagocytosis by endothelial cells and histiocytes operate to remove subintimal lipids which constantly enter from the blood stream (77). However, the mechanisms for the removal of lipid from the

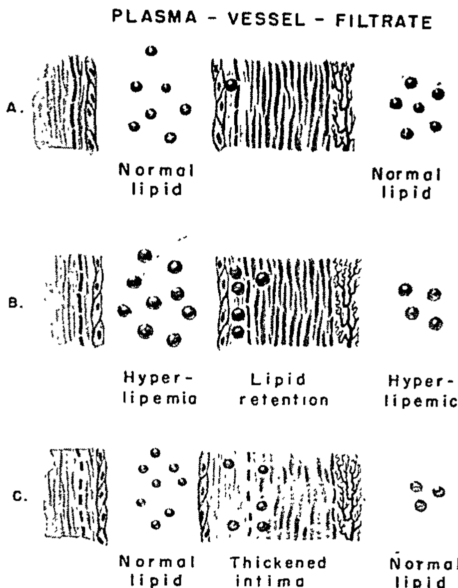


Fig 12 Schematic representation of filtration theory of atherogenesis (A) Normal plasm [illegible] elasti [illegible] (B) [illegible] mal plasma lipids passing through an arterial wall with thickened intima and fragmented internal elastic lamina (Courtesy Dr Irvine H Page and *Circulation* (80).)

persons), hydropic swelling of the intimal endothelial cells of vessels of various caliber was seen. He suggests that this is due to increased permeability preceded by physico-chemical disturbances of plasma colloids. Then follows seepage of plasma through the defective endothelium which causes edema and hyaline-mucoid changes of the subintima. After the breakdown

done in elucidating whether this relationship between serum cholesterol and atherosclerosis also holds for man (43-46, 109, 112, 114, 117, 128, 130-147, 260, 291).

TABLE 2

AVERAGE VALUES OF CONSTITUENTS OF INITIAL LESIONS

Type of Lesion	*Moisture**	*Total lipid*	*Cholesterol Free*	*Cholesterol Ester*	*Phospholipid*	*Galactoside*	*Fatty Acids, Neutral Fat, etc*	*Calcium*
Normal intima	71 6	14 4	14 2	38 6	20 1	8 0	19 1	0 23
Early fatty plaques	67.5	25 9	16 2	38 5	19 0	5 8	20 5	0.86
Fibrous plaques	66 5	27.2	18 1	47 5	14 9	4.5	15 0	3 94
Calcified Tissues	38 6	12 8	21 9	47 2	13 2	4 6	13 1	24 3
Atheromatous ulcers	60 8	36 0	27 2	42 1	16 0	4.3	10 4	10.1

* Moisture expressed as per cent of net weight, total lipid and calcium as per cent of dry

Table 10, p 98

Phospholipid-Cholesterol Ratio: Hueper contended (127, 148) that atheromatosis might not be due to hypercholesterolemia but to a disturbance in the stabilization of the colloid state of cholesterol in the blood by factors favoring the precipitation of the cholesterol in plasma and tissues. The hydrophobic insoluble cholesterol is able to be carried in colloidal suspension in high concentration in the serum because of the presence of the hydrophilic substance, phospholipid. Phospholipids and cholesterol exist in human blood sera in an equimolar ratio. The phospholipids keep the cholesterol stabilized in the colloidal form Increases in phospholipid are not disturbing to this chemical state, but on the other hand, increases in cholesterol beyond the equimolar state alter the colloidal stability of the lipid emulsion The genesis of arteriosclerosis has been linked, therefore, not to the elevation of the serum cholesterol concentration per se but to abnormal ratios of cholesterol to phospholipids.

Davidson and his associates (149) studied the ratio of the phospholipids to cholesterol in dogs given 0 6 gm. of thiouracil daily and fed a ration ad libitum containing 5 per cent cholesterol. This resulted in a hyperlipemia in the range of 1,000 to 5,000 mg per cent The phospholipid increased at the average ratio of one mol of phospholipid for every 5 mols of cholesterol. In young dogs on a normal diet the molar ratio of cholesterol and phospholipid was approximately 1.1.

Further, Kellner and his group (150, 151) studied the effects of intravenous detergents (Tween 80 or Triton A-20) on experimental arteriosclerosis in the rabbit. Rabbits fed cholesterol and given intravenous detergents had far higher mean levels of blood cholesterol but significantly less arterio-

arterial wall are not adequate to dispose of the lipids constantly penetrating through the endothelial membrane. Over the years and with advancing age, increased accumulation of lipids occur subintimally (47).

Page (80) [Figs. 12 and 13] tabulates six factors in the relation of the arterial wall to atherogenesis as follows:

1. The anatomy, biochemistry and physiology of the vessel wall, all of which are hereditarily conditioned.
2. The composition of the plasma.
3. The lateral arterial pressure and rate of filtration.
4. The responsiveness of intimal tissues to filtered products and their degradation production, normal or abnormal.
5. The metabolic capacity of the vessel wall.
6. Changes in filtration capacity of the vessel wall, such as may result from age, hypertensive diseases and metabolic disorders.

Composition of Blood: In recent years, the cholesterol concept of atherogenesis has been the etiologic factor subjected to the most intensive investigation (37, 89-117). This concept will be detailed in the next section.

BIOCHEMISTRY OF ARTERIOSCLEROSIS

This may be reviewed from two points of view: (1) the analysis of chemical changes in arteriosclerotic vessels, and (2) the chemical composition of the blood in atherosclerosis (118).

The Arteries: Several reports indicate (119-122) that the arteriosclerotic aorta has a higher cholesterol content than the normal vessel. Weinhouse and Hirsch (122) showed that lipid and calcium contents of the media of the human aorta increase with age In Table 2 the lipid and calcium composition of the normal intima is compared with that in various intimal lesions The proportions of free and ester cholesterol rise with the increasing severity of atherosclerosis while the total phospholipid decreases slightly and the calcium rises.

The Blood: The first question arises as to whether the lipid content of the blood and the intima are the same This is in direct relation with the belief that deposition of lipid in the atheromatous plaques of the intimal layer is related in some manner to the lipid compositions of the blood (123-125). Weinhouse and Hirsch (122) pointed out that the proportions of free cholesterol, cholesterol esters, phospholipids, and neutral fat in the plasma were strikingly similar to those in the normal intima and in the early intimal plaques.

The relation of serum cholesterol to atherosclerosis was based on animal experiments (42, 110, 126-129, 257, 258, 259) in which feeding cholesterol has produced a rise in serum cholesterol associated with the deposition of atheromatous plaques in the aorta and blood vessels. Much work has been

uric acid in its lactum state may be a powerful cationic surface agent, and perhaps attach itself to a larger cholesterol molecule and bring the cholesterol molecule into contact with a surface such as arterial intima."

Jackson and Wilkinson (159) doubt the usefulness of the phospholipid cholesterol ratio as an index of atherosclerosis.

Macrochylomicronemia: Moreton (160, 161) places emphasis on the role of neutral fat hyperlipemia after meals as a source of atherogenesis. "The cumulative effect of many fatty meals over a lifetime, by producing these transient showers of lipid particles in the plasma, may be the underlying cause of intimal lipid deposition in human atherosclerosis. . . . The increased particle size of the lipids in sustained or alimentary hyperlipemia is the stimulus to the phagocytosis in the intima by macrophages and the formation of the typical 'foam cells.'"

Zinn and Griffith (162) and Becker, Meyer and Necheles (163) have supported this concept Zinn and Griffith found a significantly greater ratio of macrochylomicrons to microchylomicrons in the fasting blood sera of atherosclerotic patients, as compared with control subjects.

Lipoprotein Molecules: An explanation of the presence of arteriosclerosis in patients with either normal or high levels of blood cholesterol has been offered by Gofman and his associates (99, 105, 164-167). They suggest that a defect in the giant molecules in the serum (cholesterol, cholesterol esters, phospholipids, fatty acids and protein as the building blocks) might be responsible for the development of arteriosclerosis rather than the mere analytical level of these components in the serum. The ultracentrifuge was used to characterize certain physico-chemical properties of these molecules in their native state The lipoprotein of normal rabbits ultracentrifugally appears as a single component of flotation rate of 5 to 8 Svedburg units On feeding 3 gm. of cholesterol per week, in some rabbits a series of new cholesterol-bearing giant molecules appeared in the serum which could be differentiated from those in a normal rabbit by their flotation rate (S_f class 10-30) and by a difference of their hydrated densities After 15 weeks of cholesterol feeding, the entire group of rabbits was autopsied Rabbits failing to develop high levels of the components of S_f greater than 5 to 8 units showed no gross or only minimal atherosclerosis, whereas mild to severe atherosclerosis developed in rabbits with high concentrations of the molecules of the S_f 10-30 class.

In a study of 600 human sera (98), a low density lipoprotein of S_f value between 3 and 8 units was found in all In some sera low density lipid and lipoprotein components with flotation rates in the S_f 10-20 class were found Analyses of sera for this latter molecule were made in groups of men and women with no known disease, from 20 to 40 years of age and from 40 to 70 years of age. The incidence of measurable concentrations of molecules

sclerosis than control animals on the same cholesterol diet without the detergent. The blood phospholipid in the experimental group of rabbits was elevated in the same range as the cholesterol, whereas in the control animals, phospholipid concentrations were invariably much lower than those of cholesterol

Katz (107) has found in the chick that cholesterol induced arteriosclerosis is usually associated with both hypercholesterolemia and elevated C/P ratios

Ahrens (152, 153) pointed out that in primary biliary cirrhosis, the serum lipid pattern is such that the predominance of phospholipids is pronounced while in hyperlipemic states other than biliary obstruction cholesterol esters or neutral fat predominate. Fasting serum in primary biliary cirrhosis is always clear while in the hyperlipemic conditions, such as nephrosis, hypothyroidism and essential xanthomatosis the serum is milky. The reason for the occurrence of these two types of sera lies in the ratio of phospholipid to total lipids, the higher phospholipid content in primary biliary cirrhosis serving to keep the fats in solution

Morrison, Gonzales and Wolfson analyzed the ratios of serum phospholipid and total cholesterol in relation to atherosclerosis (154). Ninety-two normal persons had an average ratio of 1 23 with only 10 per cent of the ratios below 1.0. In 124 patients with proved coronary thrombosis and myocardial infarction, the average phospholipid-total cholesterol ratio was 0 977, and 66 per cent were below 1.0

Pomeranze and Kunkel (155) studied the phospholipid cholesterol ratios in 50 patients, 25 of whom had severe arteriosclerosis as judged by electrocardiographic evidence of coronary disease, x-ray evidence of arterial calcification, or signs of arteriosclerosis in the retina of these 25 patients. Twenty-one (84 per cent) had phospholipid-cholesterol ratios below 0.89.

Steiner, Kendall and Mathers (146) compared 82 patients with coronary arteriosclerosis with 112 healthy adults and found the serum cholesterol and serum lipid phosphorus values to be elevated in the former patients as compared with the control group. The increase in serum lipid phosphorus in the arteriosclerotic patients was not proportional to the increase in the serum cholesterol resulting in an increase in the serum cholesterol-lipid phosphorus molar ratio.

Gertler (40, 93, 156-158) has introduced the "CUP" ratio as having a possible selective and predictive value in atherosclerosis. This is based on the ratio of the cholesterol times the uric acid to the lipid phosphorus levels in the serum The mean value obtained for the healthy group was 90 and for the coronary group (patients with myocardial infarcts) 119 He states that "at present there is no satisfactory explanation as to how cholesterol and uric acid interrelate in coronary heart disease. It is possible that the

patients with myocardial infarcts as test groups (98). They found that the highest correlation occurred in the lipoprotein spectrum of the S_f 10-20, a similar correlation was also found for the S_f 12-20 class. When expressed in milligrams per cent, a level of 25 mg per cent was taken as indicating the presence of atherosclerotic activity. The clinically normal male population at age 25 years has a median concentration of S_f 12-20 molecules of 28 mg. per cent, at age 30, 39 mg per cent, and beyond 30 years of age shows no further significant change even through the sixtieth year. The clinically normal female reaches the S_f 12-20 level for the male of 30 years during her fiftieth to sixtieth years

Sera with blood cholesterol levels well below 200 mg per cent may show high concentration of molecules of S_f 10-20 class. Further, sera with high cholesterol levels well over 200 mg. per cent may not show any measurable concentration of S_f 10-20 class of molecules The authors (98) have used this variation in physico-chemical properties of the lipoprotein molecules to explain the occurrence of atherosclerosis in patients with both normal and elevated levels of cholesterol in the blood.

In 1953 (164), a value for expressing an individual's coronary atherogenic potentialities, or rate of development of coronary atherosclerosis, was determined and was referred to as the index of coronary atherogenicity. The formula is as follows:

$$\text{A I.} = \frac{\text{mg \% standard } S_f \text{ 0-12} + 1\ 75 \times \text{mg \% standard } S_f \text{ 12-100}}{10}$$

The average atherogenic index values are given in Table 3.

Eiber (168) has pointed out that total serum lipids, standard S_f lipoprotein molecule values and the atherogenic index rise steadily, in both males and females from age 20 until approximately age 65 and 75 years, after which there is a steady decline until age 100 years. Cholesterol and phospholipids show no significant changes. Ackerman (262) has confirmed the finding of lipoprotein level decrease with advancing age.

Keys (110) in discussing the diagnostic value of the serum cholesterol and the serum lipoproteins in coronary patients, states that "neither measurement, however, is a good discriminator between such patients and healthy persons. If there is any advantage to one of these measurements over the other in detecting or predicting coronary disease, the evidence is in favor of total cholesterol There is no evidence that a level of G concentration in the blood may be of practical value as an indicator of the probability of present or impending coronary disease"

Microfractionation of Plasma Proteins: Barr and his co-workers (89, 92, 170) studied the lipoproteins by means of Cohn's microfractionation method number 10. By this method alpha and beta lipoproteins are sep-

in this class was significantly higher in males from 20 to 40 years of age than in the corresponding age group of females with both sexes over 40 showing significant increases over the younger age groups. Diabetic men from 35 to 70 years of age and diabetic women from 25 to 70 years of age both show a higher incidence of measurable concentrations of molecules of the S_f 10-20 class than the normal corresponding age groups (98). One

TABLE 3

AVERAGE ATHEROGENIC INDEX VALUES

Diagnosis	*Cases*	*Age*	*Sex*	*Index*
Normal	29	20-29	M	59
	284	30-39	M	70
	473	40-49	M	74
	267	50-59	M	75
	74	60-69	M	73
	50	20-29	F	46
	188	30-39	F	51
	140	40-49	F	61
	80	50-59	F	71
	9	60-69	F	84
Coronary heart disease	9	30-39	M	114
	91	40-49	M	95
	148	50-59	M	91
	61	60-69	M	84
Diabetes mellitus	32	30-49	M	86
	37	50-69	M	81
	7	30-49	F	90
	19	50-69	F	101
Hypertension*	64	30-39	M	78
	106	40-49	M	79
	104	50-59	M	78
	52	60-69	M	79
	25	30-39	F	59
	49	40-49	F	68
	89	50-59	F	72
	6	60-69	F	73

* Hypertension here includes individuals either with a systolic pressure greater than 142 mm of Hg or with a diastolic pressure greater than 92 mm of Hg
(After J W Gofman *et al* (164))
Courtesy of Dr John W Gofman and *Modern Medicine*

hundred one of 104 patients with proved myocardial infarction showed the presence of molecules of the S_f 10-20 class in measurable concentrations All categories studied showed a lower frequency of occurrence of measurable concentrations of S_f 10-20 molecules than did the patients with myocardial infarction. When diets restricted in cholesterol and fats were given, the measurable concentration of the molecules in the S_f 10-20 class was definitely reduced in 2 weeks to 1 month.

Gofman and his associates studied the correlation between levels of various serum lipoproteins and atherosclerosis using normal subjects versus

TABLE 4

LOW FAT DIET

Food	*Permitted*	*Avoid*
Beverage	Coffee, tea, skimmed milk, buttermilk	Chocolate drinks, whole milk, alcoholic beverages
Bread	All	None
Cereal	All	None
Cheese	Cottage, farmer, pot cheese	All others
Dessert	Angel food cake, fruit whips, simple puddings, gelatin, sherbet	Chocolate desserts, cakes containing nuts and frosting, ice cream, pies and pastries, nuts
Egg	3 eggs weekly	Fried in any form
Fat	None	All
Fish	Lean, baked, boiled, broiled	Fried, smoked, canned
Fruit	All fruits except avocado pears, fruit juices, tomato juice	Avocado pears
Meat	Lean, boiled, broiled, roasted	Canned, smoked, spiced meat, gravy
Potato or Substitute	Mashed, baked boiled potatoes, barley, farfel, macaroni, noodles, rice, spaghetti	Fried
Soup	Any from foods allowed	All others
Sweet	Jam, jelly, sugar, syrup, hard candy	All others
Vegetable	All except under "Avoid"	Broccoli, Brussel sprouts, cabbage, cauliflower, corn, cucumber, green pepper, lima bean, onions, radishes, turnips

Any food which disagrees with the patient should be avoided

Meal Plan

Breakfast	*Dinner*	*Supper*
Citrus Fruit	Fruit Juice	Fruit Juice
Coffee	Lean Meat, Poultry or Fish	Lean Fish, Cheese or 1 Egg
Cereal	Potato or Substitute	Potato or Substitute
Bread and Jelly	Vegetable	Vegetable
Skimmed Milk	Salad	Salad
Sugar	Bread	Bread and Jelly
	Fruit or Other Dessert	Fruit or Other Dessert
	Tea with Lemon	Skimmed Milk
	Sugar	
		Night Feeding
		Skimmed Milk

*Approximate Composition**

	Unit	*Amount*		*Unit*	*Amount*
Calories		2000	Vitamin A	I U	3000
Carbohydrate	gm	355	Thiamine	mg	1 5
Protein	gm	85	Riboflavin	mg	2
Fat	gm	30	Niacin	mg	18
Calcium	gm	1	Ascorbic Acid	mg	180
Iron	mg	15			

(From Diet Manual, Beth Israel Hospital, New York, N.Y.)
* This diet is below the Recommended Daily Dietary Allowances of 1948, in vitamin A

arated Lipids found in fraction IV+V+VI are in combination with alpha globulin and those found with I and III are combined with beta globulin A breakdown of the cholestero-phospholipid ratio in man indicates a normal value of 0.80 of plasma, 0.50 of alpha lipoprotein and 1.25 of beta lipoprotein. The per cent of total cholesterol in alpha lipoprotein is 30; the per cent of total cholesterol in beta lipoprotein is 70. Patients who have survived coronary occlusion (89) or present otherwise unequivocal evidence of the complications of atherosclerosis show a tendency to reduction of alpha lipoprotein and a relative or absolute increase in beta lipoprotein, as well as other components of Cohn's Fractions I and III. These changes may be seen without hypercholesterolemia or recognizably significant elevation of the cholestero-phospholipid ratio of the unfractionated plasma.

A method of determining alpha and beta lipoproteins by means of the ultracentrifuge has been devised by Lewis and Page (171, 171a). Paper electrophoresis may also be used to determine the lipoprotein pattern (171b, 171c, 172).

DIET AND ARTERIOSCLEROSIS

Ethnic differences in predilection to atherosclerosis has been most positively related to the quantity of cholesterol and fat in the diet. Rosenthal (173) makes a strong point for the fact that races which subsist on a high cholesterol and fat intake never have atherosclerosis absent On the other hand, where a diet high in protein is consumed, with a low cholesterol and neutral fat intake, atherosclerosis is not prevalent Members of the same race who change their locale and subsequently their diet may show a tendency to atherosclerosis where formerly no such predisposition was noted (173-176). Reports on a low incidence of atherosclerosis on a low cholesterol-low fat diet have been made for the following groups. Asians and Africans (177), Costa Ricans (178), Okinawans (179); Chinese (175, 180), Ceylonese (181), Neapolitons (182), and Bantus (183). On the other hand, the opposite has been found for those subsisting on a high fat, high cholesterol diet: the nomadic Kirghiz (184), Europeans and North Americans (177). A conflicting report was made by Rogers (185) who, on an autopsy study of the vascular structures of the population in London and Calcutta, failed to reveal any difference in the frequency and distribution of arteriosclerotic lesions, although the Indian diet was low in cholesterol. Gubner and Ungerleider (77) concluded that low levels of cholesterol may confer some protection against arteriosclerosis The evidence for this was gathered from a study in which the incidence of arteriosclerosis of the aorta was found to be approximately the same in individuals with a slight degree of hypercholesterolemia as in those with normal blood cholesterol levels, while a significantly lowered incidence of arteriosclerosis of the aorta was found in those patients with low cholesterol levels

TABLE 5

LOW CHOLESTEROL DIET

Food	*Permitted*	*Avoid*
Beverage	Coffee, tea, skimmed milk, buttermilk	Chocolate drinks, whole milk, alcoholic beverages
Bread	All	None
Cereal	All	None
Cheese	Cottage, farmer, pot cheese	All others
Dessert	Angel food cake, fruit whips, simple puddings, gelatin, sherbet	Chocolate desserts, cakes containing nuts and frosting, ice cream, pies and pastries, nuts
Eggs	2 eggs weekly	Fried in any form
Fat*	Vegetable fats and nut oils	Animal fat
Fruit	All fruits except avocado pears, fruit juices, tomato juices	Avocado pears
Meat and Fish	Lean, 4 oz daily	Liver, sweetbreads, brains, canned, smoked or spiced meat and fish, gravy
Potato or Substitute	Mashed, baked, boiled potatoes, barley, farfel, macaroni, noodles, rice, spaghetti	Fried
Soup	Any from foods allowed	All others
Sweet	Jam, jelly, sugar, syrup, hard candy	All others
Vegetable	All	None

Any food which disagrees with the patient should be avoided

* Unless caloric intake is restricted, vegetable fats, such as olive oil, margarine, mayonnaise, French dressing and fats made from nut oils may be used

Meal Plan

Breakfast	*Dinner*	*Supper*
Citrus Fruit	Fruit Juice	Fruit Juice
Cereal	Lean Meat, Poultry or Fish (2½ oz)	Lean Fish (1½ oz)
Bread and Jelly	Potato or Substitute	Cheese or 1 Egg
Coffee	Vegetable	Potato or Substitute
Skimmed Milk	Salad	Vegetable
Sugar	Bread	Salad
	Fruit or Other Dessert	Bread and Jelly
	Tea with Lemon	Fruit or Other Dessert
	Sugar	Skimmed Milk
		Night Feeding
		Skimmed Milk

*Approximate Composition***

	Unit	*Amount*		*Unit*	*Amount*
Calories		1900	Vitamin A	I U	3100
Carbohydrate	gm	360	Thiamine	mg	1 4
Protein	gm	70	Riboflavin	mg	1 9
Fat	gm	25	Niacin	mg	14
Calcium	gm	1	Ascorbic Acid	mg	179
Iron	mg	15			

**This diet is below the Recommended Daily Dietary Allowances of 1948, in Vitamin A (From Diet Manual, Beth Israel Hospital, New York, N Y)

Keys (131) pointed out that in a study of clinically healthy men of age groups 18 to 55 years, the serum cholesterol level was not significantly related to differences in the habitual cholesterol intake over a range of something like 250 to 800 mg daily. These findings add weight to the contention that there is a need for regulating the intake of cholesterol and especially of fat in order to regulate the level of blood cholesterol. In order to be absorbed, cholesterol requires the presence of fat as fatty acids. This is so because it is the esterified cholesterol that is well absorbed. Cook (126) has shown that cholesterol can be recovered quantitatively from the feces in animals on a fat-free diet. Studies on populations forced by circumstances into starvation or wartime austerity diets low in fat and cholesterol reveal a lowered incidence of atherosclerosis on autopsy (124, 177, 178, 186-188).

There are clinical studies which relate the level of blood cholesterol to an experimentally administered low cholesterol or fat restricted diet (7, 189-195) (Tables 4 and 5). Morrison (193) used 25 gm of fat, Kempner (192) and Watkin (195), 5 per cent fat, Hildreth (191), in 3 subjects, 9, 10 and 62 gm of fat All were able to lower blood cholesterol levels. Wilkinson, Blecha and Reimer (129) and Gertler, Garn and White (93) found no such reduction in blood cholesterol on a low cholesterol diet

Gofman *et al* (98) and Walker *et al.* (194) were able to show a reduction in the level of the S_f 10-20 lipoprotein fraction of the serum through a reduction in weight on a reducing diet.

Keys (134) says, in summary, "we may remark that direct evidence of the effect of the diet on human atherosclerosis is very little and is likely to remain unsatisfactory for a long time. But such evidence as there is, plus valid inferences from indirect evidence, suggests that a substantial measure of control of the development of atherosclerosis in man may be achieved by control of the intake of calories and of all kinds of fats, with no special attention to the cholesterol intake. This means· (1) avoidance of obesity, with restriction of the body weight to about that considered standard for height at age 25, (2) avoidance of periodic gorging and even temporary large calorie excesses, (3) restriction of all fats to the point where the extractable fats in the diet are not over about 25 to 30 per cent of the total calories, (4) disregard of cholesterol intake except, possibly for a restriction to an intake less than 1 gm. per week."

Keys (292) indicates that the low coronary disease populations get no more than 20 per cent of their food calories from fats as a rule In contrast, the high coronary disease populations range from about 35 per cent fat calories (England) to 40 per cent (United States). What then, asks Katz (293), is the role of the diet. He answers that the ingestion of an unbalanced diet rich in cholesterol and lipids and calories over the years results in significant atherosclerosis in a sizable proportion of the population. How-

centration of serum cholesterol, phospholipids, and phospholipid-cholesterol ratio.

Betaine: Morrison (201) reported significant lowering of the serum total cholesterol and consistent rise in serum phospholipid-cholesterol ratios with betaine given to a series of 21 patients suffering from proven coronary atherosclerosis. Betaine was administered orally in an average daily dose of 6 gm

Methionine: No alteration in serum cholesterol or lipoprotein levels were noted in 24 American males with moderate to marked elevations of these levels who were given their usual diet and given 3 gm of methionine daily for 6 weeks (137).

Inositol: Felch and Dotti (197) studied the effect of inositol on the level of serum total cholesterol in 30 diabetic patients given 3 gm. of inositol daily. The medication was given for 8 weeks. In those with a high initial total cholesterol there was an abrupt fall over the first 2 weeks, then a slower decline. For example, 17 diabetics with an initial total cholesterol over 300 mg. per cent had an average drop of 69.2 mg per cent in 8 weeks, while the 13 diabetics below 300 mg. per cent had an average drop of only 29 0 mg per cent. On the other hand, (198) no effect on the blood cholesterol was noted by the administration of choline chloride (1 gm four times daily) to 6 diabetic patients with blood cholesterol levels over 350 mg. per cent.

Herrmann found that in 20 hypercholesterolemic patients given 2 gm of inositol a day for 25 to 30 days, an average drop of 19 per cent of cholesterol occurred (215).

Leinwand and Moore state that inositol, administered in doses of 1.0 gm. three times daily, without any attempt to control the diet was eventually able to produce a marked decrease in all lipids (216)

Forty patients with angina pectoris were studied (217) in a double-blind experiment testing the effect of a choline-inositol syrup on their symptoms and on their plasma lipids A randomized series was followed in starting these subjects on either the choline-inositol syrup or placebo. After 6 months on the first preparation, they were given a 3-week supply of a mixture of the two in order to minimize the slight taste difference. Then they were given the second preparation for 6 more months Each day, these subjects recorded upon a report card the relative amount of pain experienced and the number of nitroglycerin tablets taken. At 3-week intervals, they were weighed, and blood was secured for determinations of plasma cholesterol and phospholipid. The data were subjected to independent statistical analysis Choline-inositol therapy produced no significant effect upon the symptoms and the nitroglycerin intake of these subjects The mean plasma cholesterol and phospholipid levels were significantly higher while on choline and inositol, but the mean phospholipid-free cholesterol ratio was not sig-

ever, this atherogenic diet may still need other factors, acting in conjunction to result in atherosclerosis: heredity, sex, physical activity, metabolic *disease and local factors.*

ANTI-ARTERIOSCLEROTIC AGENTS

It must be stated at the outset that there is no definitive proof for the uefulness of any anti-arteriosclerotic agent reported to date in the prevention or reversal of atherosclerosis itself in the human. Two points need unequivocal proof. (1) that these agents consistently lower the total serum cholesterol, and (2) that the lowering of the total serum cholesterol has a reversal effect therapeutically on the human atherosclerotic lesion.

For the purpose of mobilizing cholesterol from the tissue depots and for speeding the hepatic removal of lipids, such lipotropic substances as choline, inositol, methionine and betaine have been used alone or in combination (196-207) Lecithin has been suggested as an anti-arteriosclerotic agent because it tends to maintain plasma lipids in a state of supersaturation in the serum and controls the degree of dispersion of the colloid lipid particles (208-209) The effects of sitosterol (210, 211) and thyroid on blood lipid levels have also been reported (212).

Choline: Choline chloride, mono or dihydrogen citrate, was given in doses of 1 gm four times daily with meals to 70 patients for from 1 to 24 months (averaging 5 months). The blood cholesterol was lowered from a mean of 288 mg per cent to 220 mg per cent (199)

Morrison and Gonzales (202, 204, 205) treated 115 patients with proved coronary thrombosis and myocardial infarction with choline after discharge from the hospital. Fifty-two patients were given choline for a year, 35 for 2 years, and 28 for 3 years. The dosage of choline varied from 6 to 32 gm. daily. A group of alternate controls was set up consisting of 115 patients with the same disease who were discharged from the hospital under identical conditions. Of the 115 control patients, 35 patients (30 per cent) had died after 3 years, 29 being due to cardiac causes. In the choline treated *series of 115 patients, 14 patients (12 per cent) had died after 3 years,* 11 being due to heart disease. These authors conclude that choline appears to exert a de-cholesterolizing effect on the atheromatous depots in the vascular walls of man.

Greenberg and Bruger (198) administered choline (4 gm daily of choline base) orally for periods ranging from 1 to 5 months to 11 patients. Their ages ranged from 29 to 57 years Nine patients had coronary insufficiency or previous myocardial infarction, or both; 2 patients were suspected of having coronary artery disease and were members of a family with a striking history of arteriosclerosis The control period lasted from 1 to 5 months and at least 3 *estimations of serum cholesterol* and phospholipids were done. The results indicated that choline therapy was without effect on the con-

significant drop in the serum cholesterol level. The solution contained 500 mg. of polysorbate 80, 500 mg. of choline dehydrogen citrate, and 250 mg. in each 5 cc. of the solution.

Goldbloom, Eiber and Boyd (286) assessed the value of lipotropic agents in atherosclerosis. Fifty patients with clinical generalized atherosclerosis and chronic artery disease were maintained on a low-fat, low cholesterol diet for 36 months. Twenty-five of these patients were given therapeutic dosages of a lipotropic preparation during this period. Serum lipid fractions such as cholesterol, phospholipids, total lipids and neutral fats were determined and averaged on all 50 patients at the onset of the study and at 6-month intervals for a period of 3 years. Except for a slight decrease in blood serum cholesterol of all the 50 patients, attributable to the low-fat restrictions of the diet, there were no significant differences in any of the other serum lipid fractions. Changes in the ratio of phospholipid to cholesterol were practically the same in the control and lipotropic group of patients. Low-fat, low cholesterol diets attained the same end result as lipotropic agents upon reducing serum lipid partitions. Based on these findings, they concluded that there was no clinical or laboratory confirmation for the value of the administration of the present known lipotropic preparations in influencing abnormal serum lipid patterns in the treatment or prophylaxis of human atherosclerosis

Blocking Agents: Blocking agents, such as sitosterol and dihydrocholesterol have been reported to have either little (210, 211, 261) or a substantial (219) affect in reduction of the lipoproteins in the serum

Joyner and Kuo (219) have shown that on an unrestricted diet, in normocholesteremic and hypercholesteremic patients fed 12 to 24 gm. of plant sterol (sitosterol) per day, that there is a significant decrease in blood cholesterol level This decrease is related to the dose of sitosterol, less than 10 gm. daily having no effect Best *et al* (220) found a mean fall of 16 4 per cent of serum cholesterol in patients (mainly hypercholesterolemic) fed 15 to 18 gm. of beta sitosterol per day by mouth These same authors (287) confirmed the serum cholesterol lowering effect of 20 to 25 gm of sitosterol daily. Effects on the lipoproteins were less consistent

Ahrens, Blankenhorn and Tsaltas (221) reported that on an isocaloric diet, the substitution of plant fats for animal fats will cause a 20 per cent decrease in total serum cholesterol.

Thyroid: The effect of a daily dosage of 3 grams of dessicated thyroid on serum lipoproteins was studied by Strisower *et al* (212) in 50 schizophrenic patients. The S_f0-12 and the S_f12-20 levels were significantly reduced within a period of 3 weeks, but by 24 weeks the S_f0-12 concentration had returned to the pre-thyroid level. The magnitude of the drop was directly related to the pre-thyroid value.

nificantly altered. Fluctuations of total cholesterol and of phospholipid were not affected by choline-inositol therapy.

Lecithin: Adlersberg and Sobotka (208) treated 5 cases of xanthomatosis and hypercholesterolemia with 12 to 15 gm. of soybean lecithin daily. There was a lowering of serum cholesterol in all patients and in one patient it fell from 1,420 mg. per cent to 445 mg. per cent.

Twenty-five gm. of "soya lecithin" fed daily to 7 patients for 6-week periods and to 1 patient for a 10-week period by Steiner and Domanski (45) resulted in an average fall of 68 mg. per cent of serum cholesterol. The decline, however, could be maintained for only five weeks despite continued administration of the "soya lecithin"

Goulder, Kissane and Bohl (218) placed 25 patients with angina pectoris on Granulestin, a concentrate of purified soy phospholipids consisting of lecithin, cephalin and liposital made by the Associated Concentrates, Division. American Lecithin Co. Granulestin was given in doses of 1 heaping tablespoon per day, or about 20 gm Clinical improvements, as measured by reduction of nitroglycerin intake and, not objectively, occurred in 24 per cent of the group Improvement occurred only after a month of treatment. Once treatment was discontinued, the clinical state returned to the pretreatment picture in irregular fashion, in some instances over a period of several months. Serum cholesterol levels decreased only slightly during treatment Serum phospholipid concentrations decreased rather definitely to effect an increase in the serum cholesterol-serum phospholipid ratio. Since placebo therapy can improve anginal symptoms 40 per cent, the improvement on Granulestin cannot be considered significant.

Mixed Lipotropic Agents: A combination of choline, inositol, methionine and vitamin B complex (Methischol) was found to be more effective in reducing chylo and lipomicron counts than choline or inositol alone (204). This same lipotropic agent (205) consisting of 3 gm. of choline, 2.25 gm. of inositol, 3 gm. of methionine, vitamin B-12 and natural B complex obtained from 24 gm of liver was administered orally every day for 6 months to a series of 28 patients with coronary thrombosis and infarction. They were also placed on a 23 gm low-fat, low-cholesterol diet. Subnormal serum phospholipid cholesterol ratios below 1.0 were restored to normal levels above 1.0. Morrison believes that this was accomplished by reducing the exogenous dietary fat and cholesterol intake to lower the serum cholesterol and by increasing the exogenous source of phospholipids through the ingestion of adequate amounts of lipotropic substances, serum phospholipids were elevated.

The effect of a polysorbate 80-choline-inositol complex (Monichol) on the serum cholesterol in 16 hypercholestenemic patients was reported by Sherber and Levites (207). In 15 of the 16 patients studied, there was a

significant drop in the serum cholesterol level. The solution contained 500 mg. of polysorbate 80, 500 mg. of choline dehydrogen citrate, and 250 mg. in each 5 cc of the solution.

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SEX AND ARTERIOSCLEROSIS

The predominance of coronary artery disease in males over females (72, 73, 222), before the sixth decade has suggested the arteriosclerotic protective action of estrogen (91, 128, 158, 223-226). This same "safe period" for females is reflected in the lipoprotein studies of Gofman (105): "Both young men and young women show similar patterns of lipoproteins and low levels of S_f12-20 lipoproteins up to 25 years of age, although there has been some increase from the levels of the 0-15 year old group The male population from 25 to 30 years undergoes a striking transformation which elevates the S_f12-20 level from a median concentration of 28 mg per cent to 39 mg. per cent Beyond 30 years of age the clinically normal male population shows almost no further significant change even through the sixtieth year. The normal female does not show the striking change from 26 to 30 years of age that is seen in the male The female population increases slowly and steadily in the S_f12-20 level over the entire 25 to 60 year age span A level essentially identical with that attained by the male population by 30 years of age is reached by the female during the 50 to 60 year decade."

Barr (92, 170) finds by the microfractionation technic that women have a cholesterol-phospholipid ratio which is lower than that of men of their own age and that they have a greater proportion of their cholesterol in the form of alpha lipoproteins, which make women in these respects superior to men.

The effects of estrogens have been taken up from several different points of view. The first deals with the influence of estrogens on lipoproteins in atherosclerosis. Barr, Russ and Eder (91) find that in patients with advanced atherosclerosis and with demonstrable abnormalities in lipid concentration and distribution, the administration of estrogens is accompanied by changes in the distribution of total plasma cholesterol in the form of alpha lipoproteins which is increased and the percentage in the form of beta lipoproteins correspondingly diminished There is also a tendency for reduction in the concentration of the total cholesterol of the plasma. With withdrawal of estrogens, all opposite effects result Eighteen patients were involved The distribution of cholesterol and lipoproteins in various groups is shown in Table 6 In 11 of the group the synthetic estrogen, *estinyl* (estradiol) was given by mouth in doses of 1.0 mg (10,000 rat units) each day. In the others, *premarin* (estrone sulfate) was given in approximately equivalent rat unitage (15 mg. daily). The dose was enough to produce considerable development of the breasts and to cause temporary loss of sexual desire and potency after 3 to 4 weeks

Gertler, Hudson and Jost (223) studied the serum lipids of 25 men (aged 47 to 71 years) with carcinoma of the prostate, who were subjected to bilateral orchiectomy and then given 500 mg. diethylstilbesterol orally

daily for periods of from 3 to 28 weeks. An immediate significant rise in the serum lipid phosphorus occurred but insignificant changes occurred in the serum total cholesterol and neutral fat. As a result, there was a striking decrease in the total cholesterol/lipid phosphorous ratio Glass *et al* (227) indicated that estradiol given to 16 males and 15 females (age range of 55 to 65 years) in daily doses of 0.25 to 0.75 mg. for periods of 2 to 4 months had no marked or sustained effect on any of the serum lipid factors nor in the cholesterol-phospholipid ratio, nor did analysis of the S_f 12-20 lipoproteins show any consistent trend.

Gitman and Greenblatt (224) administered estrogen (premarin) intravenously (0.05 to 0.1 mg /kg. body weight) for various periods in 3 patients

TABLE 6

Distribution of Cholesterol and Lipoproteins by Age and Sex

Subjects	*Age Total*	*Cholesterol mg %*	*Percentage of Total Cholesterol in Alpha-Lipoprotein*	*Percentage of Total Cholesterol in Beta-Lipoprotein*
Normal women	18-35	187	34 3	61 8
Normal men	18-35	197	25 2	72 0
Normal women	45-65	252	23 4	75 0
Normal men	45-65	239	22 9	75 3
Survivors of Myocardial Infarction	28-64	259	13 6	83 9

(After Barr, D P, Russ, E M, and Eder, H A (91))
Courtesy of Dr David P. Barr and *Transactions of the Association of American Physicians*

with cardiovascular disease, and noted a fall in the level of serum beta lipoproteins of the S_f 12-20 and 20-100 classes Marett and Vivas (225) administered 5 mg of oral estrogen (premarin) daily to 17 men and 1 woman for 2 to 25 weeks. A decrease in cholesterol and total lipid level occurred in all but two men in the second to tenth week. However, with continued therapy or even cessation of therapy, the cholesterol and total lipid levels began to return to pre-treatment levels

Wuest, Dry and Edwards (227a) studied the relation of estrogens to atherosclerosis from a different point of view. The degree of coronary atherosclerosis in 49 hearts obtained from bilaterally oophorectomized women was compared with the degree of sclerosis in 600 hearts from women and in 600 hearts from men of comparable ages In general, the degree of coronary sclerosis in the bilaterally oophorectomized women was greater in the control women but less than in the control men. Rivin and Dimitroff (227b) reviewed the autopsy records of castrated women, women with breast carcinoma and estrogen-treated men with reference to the degree of atherosclerotic disease. These findings when compared with those in similar groups of men and women whose estrogen supply was considered normal, revealed that the male treated with estrogen has less atherosclerosis

than the normal male, that the oophorectomized female has an incidence of severe atherosclerosis approaching that of the male and that the hyperestrogenic female with breast carcinoma has less atherosclerosis than the normal female.

Stamler, Pick, and Katz (228) issued a preliminary report on the efficacy of estrogens in the treatment of human coronary atherosclerosis. Sixty-nine males under 50 years of age who recently had a single proved myocardial infarct were studied. They were divided into two groups on a "double blind" basis—estrogen-treated and placebo. Analysis of these groups as of June 30, 1954, revealed them to be practically identical: Mean age, 40.6 and 40 0 years, mean initial weight, 168 5 and 161.3 pounds; mean duration after infarct when study was begun 5.4 and 3 6 months, mean duration of treatment, 8 3 and 6 6 months (maximum: 19 and 18 months); mean pretreatment plasma cholesterol level, 237 mg. per 100 cc. and 261 mg. per 100 cc., mean pretreatment plasma total cholesterol-lipid phosphorus (C/P) ratio, 21.8 and 23 4 mg. per 100 cc Oral estrogen dosages were increased stepwise from an initial level of 1.25 or 2 5 mg. of mixed conjugated equine estrogens (Premarin) to 4.0-10.0 mg Estrogens tended to induce gynecomastia, loss of libido and impotence—side effects which only rarely resulted in discontinuation of therapy. The 1 25 to 4.0 mg. dosages had no effect on plasma total cholesterol levels. Higher dosages tended moderately to lower the plasma C/P ratio.

As of June 30, 1954, in the placebo group of 26 patients under treatment for 2 months or longer, a second proved myocardial infarction had occurred in 6, with 3 fatalities. In contrast, in the group of 39 under estrogen treatment for 2 months or longer, no recurrence of myocardial *infarction had* occurred. Neither the size of the groups nor the duration of treatment justifies any definite conclusions concerning the significance of these initial observations. In their second interim report (294) in March, 1956, there were 3 deaths in 49 control patients and 1 death in 53 treated patients

Steiner (229) administered 0 25 to 1.0 mg of ethinyl estradiol daily to patients with coronary atherosclerosis and to control subjects and found consistently a fall in the cholesterol-phospholipid ratio due to lowering of the serum cholesterol level in 5 instances and increase in phospholipid levels in 5 other experimental periods. There was no change in the incidence of chest pain or in the electrocardiogram in the patients with coronary arteriosclerosis during the period of observation.

Androgens, according to Barr (170) whether administered alone or simultaneously with estrogens, will increase the total serum cholesterol level.

It is to be noted (230) that estrogen reverses coronary atherosclerosis in cockrels previously induced by cholesterol feeding, despite continued

feeding of the cholesterol diet and that the estrogen-induced regression occurs in the presence of continued marked hypercholesterolemia, a reversal of previously elevated total cholesterol-lipid phosphorus ratios to normal levels, and of persistent aortic sclerosis.

Summary Statement on Therapy: Much controversy still exists relative to a specific agent for the treatment of atherosclerosis. Keys' (134) attitude toward the diet in atherosclerosis has been given on page 28. Dock (231) favors a high protein, low cholesterol, low fat diet. Dock (231) summarized the attitude of a panel of experts in this field toward all therapeutic modalities in atherosclerosis as follows. "So it appears that our panel consists largely of therapy nihilists. They have no treatment for the management of atherosclerosis in blocking agents, hormonal therapy or in lipotropic agents They feel that nothing has been shown in man about the role of cholesterol in the diet so that you don't need to lower the cholesterol fraction of your intake"

RACE AND ARTERIOSCLEROSIS

This comparison refers to predilection for atherosclerosis among races with a similar dietary background rather than that occurring with variable diets (see diet and arteriosclerosis). The statistics from the United States would indicate that coronary arteriosclerosis, coronary thrombosis and myocardial infarction are on an absolute basis less common in Negroes than in whites on post-mortem analysis (232-235). This has also been true with respect to clinical findings unrelated to coronary disease (236). Hypertension, however, is more frequent in the Negro. Weiss and Gray (237) conclude from their studies on Negroes admitted to the Louisville General Hospital, that infarction of the myocardium is infrequent in this group in the absence of hypertension Eighty-seven and one-half per cent of the males with myocardial infarction in their group had associated hypertension

McVay and Keil (288) reviewed the clinical records of 330 patients with myocardial infarction admitted to a midsouthern university hospital where the ratio of admissions was approximately 70 per cent Negro and 30 per cent white. Male and female admissions within each race was essentially equal The diagnosis of myocardial infarction was established by either necropsy findings or by electrocardiographic changes. Myocardial infarction was found to be as frequent among Negro men and women, while among the white patients it occurred three times as frequently in men The Negro woman had her infarct at an average age of 55 years, as compared with 65 years for the white woman, 61.7 years for the Negro man, and 62.7 years for the white man. Such associated illnesses as obesity, diabetes, hypertension as well as a family history of cardiovascular disease

occurred with about equal frequency in Negro and white patients Angina was more than twice as frequent in white women than Negro women The equal incidence of infarction in Negro men and women would cast some doubt on the hormonal factor in atherosclerosis, at least in the Negro population.

HYPERTENSION AND ARTERIOSCLEROSIS

Some aspects of this association have already been touched upon under the subject matter dealing with the pathogenesis of arteriosclerosis Numerous correlated studies (238-242) show two results: (1) the development of coronary sclerosis is favored by pre-existing hypertension, and (2) sclerosis is more severe among hypertensives than non-hypertensive persons The clinical picture in a hypertensive patient, then, may be dominated by the symptoms associated with coronary atherosclerosis, that is, angina pectoris or myocardial infarction This is in keeping with the statistical observations (239, 243) that 35 per cent of hypertensive hearts have a severe degree of coronary arteriosclerosis, 55 per cent a moderate and 10 per cent no notable coronary arteriosclerosis.

Because the presence of hypertension predisposes to atherosclerosis, consideration at present must be given to the use of hypertensive agents as part of the general regimen for the therapy of atherosclerosis in the presence of high blood pressure, Corcoran, Dustan, Lewis, and Page (289), on the basis of their observations of cerebral complications due to atherosclerosis in the presence of hypertension, infer that severe hypertensive disease should be vigorously treated with antipressor drugs as soon as the condition is recognized with the hope of preventing the atherosclerotic disease

DIABETES MELLITUS AND ARTERIOSCLEROSIS

There is a high clinical association of diabetes and arteriosclerosis (238, 244-253) but whether diabetes predisposes to arteriosclerosis or vice versa, as contended by Moschcowitz (168) remains unproved. Nathanson (247) found severe coronary sclerosis in 41 of 100 autopsied diabetics as compared with 8 per cent in 250 non-diabetic subjects in the same age group. Warren (251) states that the diabetic not only has a more severe degree of arteriosclerosis but the lesions developed 10 or 12 years earlier than the non-diabetic The Feldmans (253) in their post-mortem studies found coronary occlusion twice as prevalent in the diabetic as in the non-diabetic. Liebow and Hellerstein (254) have summarized several post-mortem reports on the occurrence of coronary arteriosclerosis in diabetics and non-diabetics. Their data present incontrovertible evidence indicating an *increased* incidence and severity of atherosclerosis in diabetics with the duration of diabetes as the greatest single factor in the occurrence of coronary arteriosclerosis.

In a clinical report, Liebow, Hellerstein and Miller (255) surveyed 383 living, out-patient diabetics. Forty-two per cent had arteriosclerosis heart disease (age over 40 years). An additional 16 2 per cent had arteriosclerosis of the aorta and angina pectoris was found in 10 2 per cent, 6.8 per cent had myocardial infarction. The prevalence of arteriosclerosis heart disease was related in a positive manner to sex, age and the presence of hypertension but not to the total serum cholesterol, the degree of control of the diabetes, the patient's weight, the daily insulin dose or the duration of diabetes. Dolger (256) feels that cardiovascular disease is part of the diabetic process rather than a complication of it. Boas (252) found a common association of diabetes and arteriosclerosis in his study of 500 diabetics over age 40 In a group of 282 patients whose diabetes began between 15 and 30 years of age, Root Linden and Zanca (249) found some form of vascular disease in 71 per cent Those followed less than 10 years had 21 per cent calcification of their arteries by x-ray; those followed 20 years showed 58 per cent calcification in the legs, pelvis or aorta

CORNEAL ARCUS AND ARTERIOSCLEROSIS

The corneal fatty ring has been called corneal arcus, arcus senilis and gerontoxon and is seen in all age groups When fully developed (263), it forms a white circle around the cornea and is separated from the limbus by a lucid zone The relationship between arteriosclerosis and corneal arcus has been made for at least a century but statistics for (264-268) and against (269-272) their clinical correlation are still being reported Forius (263) investigated the relationship between the serum lipids and arcus and found that in young persons, arcus is associated with extensive lipidochemical alterations in serum, while in elderly persons, local senile changes are mainly responsible The frequent co-occurrence of arcus and xanthomatosis has been noted in families with familial hypercholesterolemia (273, 274).

XANTHELASMA, XANTHOMA AND ARTERIOSCLEROSIS

Xanthelasma, the yellowish, plaque-like tumor on the eyelid, has been related to arteriosclerosis (275) and to arcus (268, 273) Some success in removal of the fatty deposits have been achieved by a low fat, low cholesterol diet More recently, Robinson (276) treated 35 patients with subcutaneous injections of from 30 to 1,000 mcg of vitamin B_{12} at weekly intervals for from 6 to 20 weeks, and beneficial results were obtained in 31 patients Improvement was noted by the end of the third week, and by the end of 6 weeks almost all lesions were flat

The relationship between xanthoma, coronary artery sclerosis and hypercholesterolemia, has been considered under the subject of heredity (see page 12) Thannhauser (277) indicates that the vascular xanthoma of

familial hypercholesteremic xanthomatosis is a localized process similar to that of skin xanthoma. Stretches of layers of xanthoma cells pile up over or beneath the inner lining of the blood vesseel. The elastic ground substance is not primarily affected. The atheroma may soften and cause coronary occlusion. On the other hand, arteriosclerosis, in contrast to familial hypercholesteremic xanthomatosis, primarily involves the elastic structures and their ground substance and the precipitation of fatty material, especially of cholesterol, is a secondary process not dependent on the cholesterol level of the serum but related to the physical properties of the altered tissue and of the colloidal solutation of cholesterol and fatty substances imbibing the altered structure of the vascular walls

Skin xanthoma have been treated with a cholesterol free diet (278), local injection of 1 cc or 5,000 units of heparin sodium solution within and under the lesions (279), by prolonged administration of heparin by intramuscular injection (280, 281), and by administration of estrogens

INTRAMUSCULAR VESSELS AND ARTERIOSCLEROSIS

Arteriosclerosis does not usually involve intramuscular arteries (282, 283) and then only affects the larger arteries Intramuscular arteries are predominantly small and do not share in the generalized arteriosclerotic process

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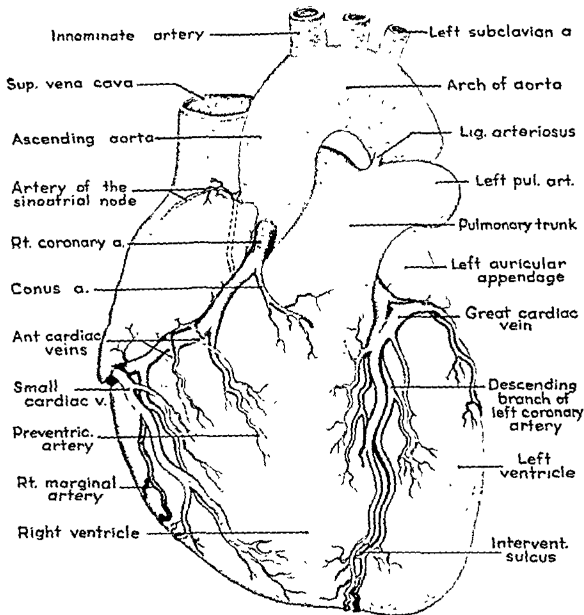


Plate I. Ventral view of the heart (From Gould, S E *Pathology of the Heart* Courtesy of Charles C Thomas, Publisher, Springfield, Illinois)

Chapter II

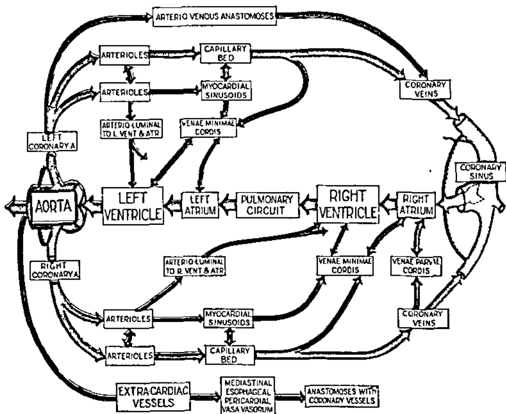
Cardiac Aspects of Arteriosclerosis

BLOOD SUPPLY OF THE HEART

Coronary Arteries: The left coronary artery arises in the wall of the left aortic sinus and passes laterally between the root of the pulmonary trunk and the left auricle. It soon branches into two vessels, the anterior descending branch, which runs in the anterior longitudinal sulcus to the apex of the heart, and the circumflex branch, which curves around the base of the atrium, in the coronary sulcus, and proceeds to the diaphragmatic surface of the heart. In this course the anterior descending branch gives off perforating rami into the substance of the interventricular septum and into the adjacent ventricular myocardium while the circumflex branch sends off a ramus which runs down over the margo obtusus toward the apex of the heart, as well as smaller branches to supply the root of the aorta, left auricle, and left ventricular wall (Plate I). To the left of the posterior longitudinal sulcus, adjacent to the coronary sinus, the circumflex branch joins with small arteries from the right coronary artery (1)

The right coronary artery arises from the right aortic sinus and proceeds laterally in the groove between the pulmonary cone and right atrium. It then courses, in the coronary sulcus, around the base of the right atrium to reach the posterior longitudinal sulcus It then divides, sending a large branch along the posterior longitudinal sulcus, the posterior descending branch, and a small branch to anastomose with the circumflex branch of the left coronary artery The right coronary artery gives off two sizable branches, one which descends along the margo acutus, the right marginal, and another to pass over the anterior wall of the right ventricle, the preventricular. It also gives off smaller branches to supply the roots of the aorta, the pulmonary trunk and the right atrium. A branch also supplies the sino-atrial node The posterior descending branch gives off perforating rami to supply the muscle of the interventricular septum and the adjacent ventricular walls.

Hearts may be classified into one of three groups, according to whether the right or left coronary arteries predominate (2) Group I consists of hearts in which the right coronary predominates, in Group II the right and left coronaries are balanced in distribution, and in Group III, the left coronary is dominant. In a study by Schlesinger (3), Group I made up 48 per cent of a series of 225 adult hearts; Group II, with a balanced circulation, made up 34 per cent, and the remaining 18 per cent fell in Group III, with a predominant left coronary artery.



various vascular chan-
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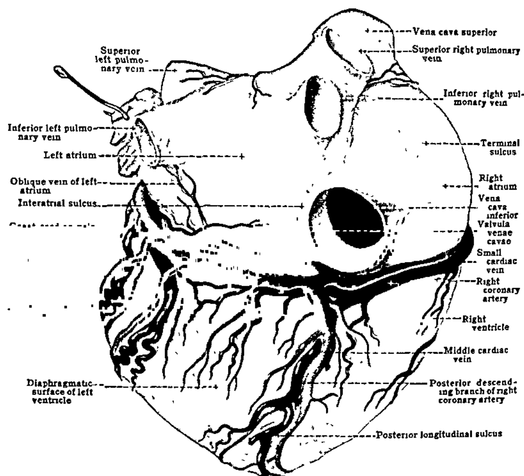
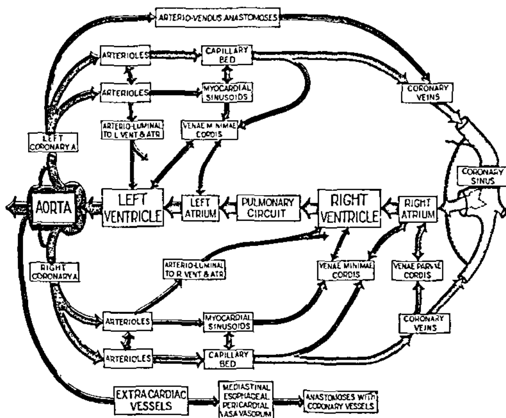


Plate II Dorsocaudal view of the heart. (From Gould, S E *Pathology of the Heart* Courtesy of Charles C Thomas, Publisher, Springfield, Illinois)



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Pathology of the Heart

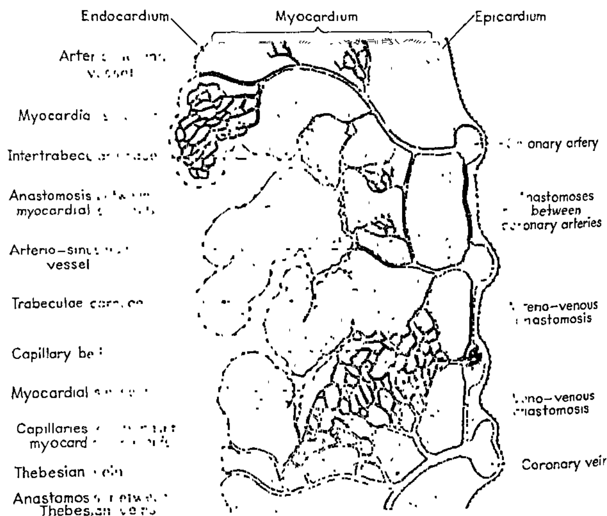


Plate IV Diagram of the ventricular wall, showing the relationship between the various intramural channels (From Gould, S E *Pathology of the Heart* Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.)

Coronary Veins: The coronary veins lie parallel to the branches of the coronary arteries, and return the blood to the right atrium by way of the coronary sinus (Plate II).

The great cardiac vein begins in the anterior longitudinal sulcus, proceeds to the coronary sulcus and then runs dorsally and goes around the base of the left atrium along with the circumflex branch of the left coronary artery. It empties into the distal end of the coronary sinus.

The middle cardiac vein runs in the posterior-longitudinal sulcus along with the posterior descending branch of the right coronary artery. It empties into the coronary sinus near the opening of the coronary sinus into the right atrium.

The small cardiac vein parallels for the most part the course of the right coronary artery. It receives tributaries from the walls of the right atrium and ventricle and empties into the coronary sinus near its entrance into the right atrium.

The Intramural Circulation: The heart muscle is extensively endowed with small interconnecting channels (2, 2a). One series of vessels connects branches of the same coronary artery, branches of the left and right coronary arteries, branches between the coronary veins and between the coronary arteries and the coronary veins. There are also connections between the lumen of the heart and the vessels. Those between the veins and the heart chamber are called thebesian veins. Those between the coronary arteries and heart lumen are called arterio-luminal vessels (Plates III and and IV).

Within the heart muscle there are myocardial sinusoids which receive vessels from the coronary arteries and send vessels to the coronary veins

NERVE PATHWAYS OF THE HEART

The heart is supplied with both parasympathetic and sympathetic branches of the autonomic nervous system The parasympathetic system is motor while the sympathetic system has both a motor and sensory function.

The cardiac para-sympathetic fibers are carried in the vagi and in the cranial parts of the accessory nerves that join them. The cardiac preganglionic fibers are myelinated and originate in the dorsal vagal nucleus and from a group of cells partially commingled with the nucleus ambiguus The para-sympathetic cardiac branches arise from the vagi both in the neck and thorax and divide into superior, middle and inferior vagal cardiac branches From these cardiac ganglia after synapse, post-ganglionic fibers go to the muscle of the auricle, to the sino-auricular node, to the auriculo-ventricular bundle, and to the walls of the coronary vessels

The motor portion of the sympathetic system begins in preganglionic neurons in cells in the intermediolateral column of the spinal cord These

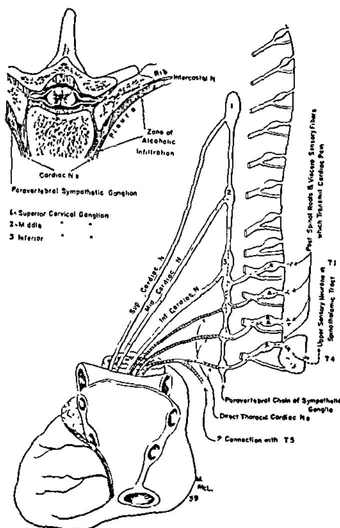


Fig 14 Afferent nerve pathways for heart and location of paravertebral sympathetic ganglia (J C White).

travel by means of the anterior spinal roots and the upper three to five pairs of white rami communicantes to enter the upper thoracic sympathetic ganglia Some of the fibers synapse in those thoracic ganglia, other fibers continue to ascend the sympathetic chain to the inferior, middle and superior cervical ganglia Both sets of fibers converge in the anterior and posterior cardiac plexuses.

The apparent pathways for pain from the heart begin in the sensory nerve endings which are present in the adventitia of the coronary arteries and in the myocardium, endocardium and epicardium (Fig. 14). The nerve fibers from these receptors collect in the superficial and deep cardiac plexuses They travel centrally by way of the middle and inferior cardiac nerves to the cervical sympathetic ganglia, and by way of the thoracic cardiac nerves to the upper four or five sympathetic ganglia Since there are no

white rami which connect the cervical sympathetic chain and the spinal cord, it has been generally assumed that these cardio-sensory fibers must pass down the sympathetic chain to the upper thoracic sympathetic ganglia and from there proceed through the white rami communicantes of the first thoracic and upper four or five intercostal nerves to reach their cell bodies in the posterior root ganglia Thus, the first neuron in this apparent system has its cell origin in the dorsal root ganglion and its synapse in the dorsal horn

Wolff and Hardy (2b) trace noxious impulses giving rise to pain after entering the cord as follows: "They are conveyed across to the opposite side where their pathways are localized in the anterolateral portion of the spinal cord The fibers of the spino-thalamic tract pass into the nucleus centralis posterior to the thalamus The cortical projection from the nucleus centralis posterior is predominantly to the post-central convolution"

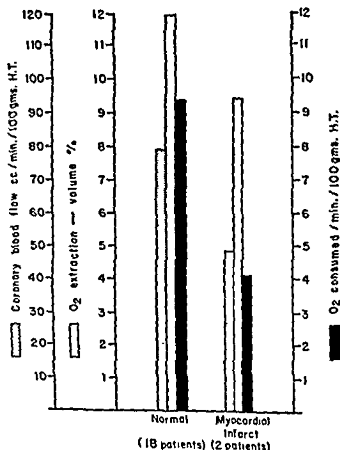


Fig 15 Results obtained in 3 patients with myocardial infarcts. The oxygen extraction and oxygen consumption, as well as the coronary blood flow per unit left ventricular tissue are reduced (Courtesy Dr Richard J. Bing and *Bulletin of the New York Academy of Medicine* (4))

CORONARY CIRCULATION AND ARTERIOSCLEROSIS

Bing (4, 4a, 4b) has studied the coronary circulation by means of coronary sinus catheterization. He has applied the same principles to coronary blood as Kety and Schmidt had to cerebral blood flow. In principle the method of Bing consists in the introduction of an intracardiac catheter through the right auricle into the coronary sinus and the withdrawal of coronary sinus blood during or after saturation of the heart muscle with nitrous oxide. Once the catheter has been placed in the coronary sinus, the heart is saturated with 15 per cent nitrous oxide. Simultaneous samples of arterial and coronary vein blood are drawn and the N_2O contents during the saturation or, preferably, the desaturation with nitrous oxide are plotted. The flow per unit of heart muscle is then calculated

The average coronary blood flow through 100 gm. of left ventricular muscle tissue is 77 cc. The oxygen consumption of this unit muscle is 9 4 cc. oxygen per minute. The average oxygen extraction is 12 volumes per cent, a figure which indicates that the oxygen extraction of heart muscle is striking, particularly when contrasted with the relative low coronary blood flow. In three patients with myocardial infarction (Fig 15), Bing has found that the oxygen extraction and oxygen consumption, as well as the coronary blood flow per unit of left ventricular tissue were reduced In congestive heart failure due to arteriosclerosis, the cardiac output and the left ventricular work is decreased but the coronary blood flow is normal. The oxygen consumption per unit of heart weight is only slightly increased in failure

THE NATURAL HISTORY OF CORONARY ARTERY DISEASE

It is well known that atherosclerosis has a predilection for the coronary arteries and that atheromatous lesions may be found even in infants and children. However, since clinical detection of coronary artery disease becomes manifest only after symptoms, such as chest pain, ensue or only after electrocardiographic changes compatible with myocardial damage are found, the natural history of coronary artery disease for statistical purposes usually begins in the fourth decade

According to the criteria of the New York Heart Association (5), arteriosclerosis of the coronary arteries with narrowing may manifest itself in one or more ways, among the more frequent are: anginal syndrome, cardiac insufficiency, paroxysmal dyspnea, paroxysmal pulmonary edema, cardiac arrhythmia and electrocardiographic abnormalities. Changes in the electrocardiogram indicative of myocardial damage include abnormalities of the QRS group, the T wave or both.

Correlation with Age: Adlersberg and Zak (6) compared 50 patients in the age groups 27 to 46 years with coronary atherosclerosis, with 50 patients

in the age group 60 to 83 years. The younger group differed from the older group in the following respects: A frequent familial occurrence of heart disease, shorter duration of anginal pain and congestive heart failure before death; a greater preponderance of males; a high incidence of heavy smokers; a lower incidence of hypertension and diabetes, and a higher level of serum cholesterol

Correlation with Sex: The sex incidence of coronary atherosclerosis was analyzed in a parallel pathological study of 600 hearts in males aged 30 to 89 years by White, Edwards and Dry (7) and 600 hearts of women, 100 in each decade from 30 to 89 years by Ackerman, Dry and Edwards (8) (Fig. 16). The severity of the arteriosclerosis was greater in men than in women; after the seventh decade, the average grade of sclerosis in men was only 13 to 17 per cent greater than in women This would indicate that symptoma-

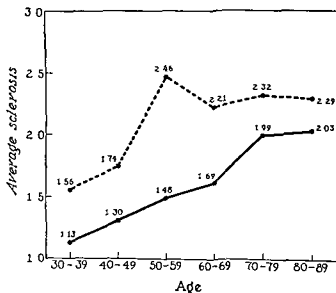


Fig. 16. Comparison of the average grades of coronary atherosclerosis in men (dotted line) and women (solid line). (Courtesy of Dr R F Ackerman and *Circulation* (8))

tology would begin earlier in men because of the earlier incidence of severe atherosclerosis. The grading of atherosclerosis is shown in Fig 17. In 59 of the 100 women, clinical coronary artery disease was diagnosed; 52 were over 60 years of age This corresponded with an average grade of coronary atherosclerosis of 1 69, a figure present in men between 40 to 49 years of age.

Underdahl and Smith (9) in the period from 1935 to 1945, found 27 women patients under the age of 40 in whom there was no reasonable doubt of the diagnosis of coronary disease This was culled from the records of 95,000 women under 40 years of age, or about 1 case in 3,500 The young-

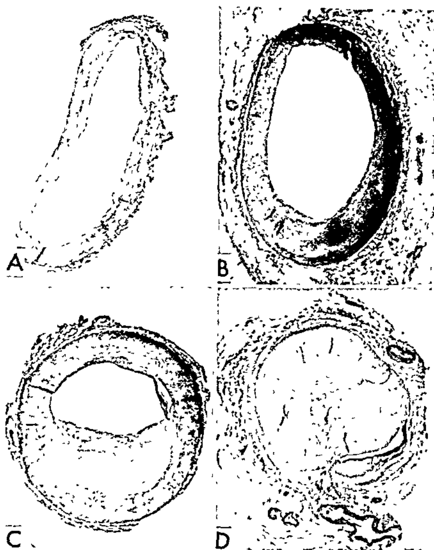


Fig 17 Examples of four grades of sclerosis in coronary arteries Sections stained with hematoxylin and eosin *a*, grade 1 (x 30), *b*, grade 2 (x 22), *c*, grade 3 (x 15), and *d*, grade 4 (x 15). (Courtesy of Dr. R. F Ackerman and *Circulation* (8).)

est patient was 30 years old From their analysis of this group, they concluded that coronary artery disease in women under the age of 40 is practically non-existent except in association with either obesity, hypertension or hyperlipemia or some combination of these conditions.

Levy and Boas (10) found in 169 cases in women with coronary artery disease, 125 or 74 per cent were associated with hypertension alone, 25, or 14 8 per cent with both diabetes and hypertension, and 6, or 3 5 per cent, with diabetes alone. In only 13 cases, or 7.7 per cent, was there neither hypertension nor diabetes. Of 1,059 men with coronary artery disease, fully 50 per cent had neither hypertension nor diabetes.

Glotzer and Wolfer (11) analyzed the clinical findings in 37 women who

had pathologic evidence of myocardial infarction secondary to coronary artery disease. The youngest was 47 and the oldest was 87 years. The average age for the entire group was 67.7 years. There were 9 diabetics in the series; the age ranged between 57 and 76 years with only 2 patients below 60 The average age was 66.7 years Eighteen patients were hypertensive with an average age of 65 2 years. Of the 37 cases, 32 (86 5 per cent) were either hypertensive, previously hypertensive, diabetic or a combination.

One may postulate that women are protected from coronary artery disease by estrogen up to the menopause and that the cessation of estrogen output plus the onset of hypertension and diabetes in greater proportion in females accounts for this peculiar natural history of coronary artery disease in women

Boas (12) reviewed the records of 124 patients with coronary artery disease under his personal observation for at least 10 years from the onset of the symptoms of heart disease. There wre 115 men and 9 women. The average age at death was 61 9 years, the average duration of the symptoms of coronary disease was 13.6 years. The age of onset of the symptoms had no apparent effect on the duration of life nor on the course of the disease The onset occurred in the fourth decade in 9, in the fifth in 63, in the sixth in 46, and in the seventh in 6 In 54 patients the symptoms began with a myocardial infarction, in 69 patients with an anginal syndrome The average duration of life, after the onset of symptoms, of those patients whose illness began with angina pectoris was 14 1 years, of those with an initial myocardial infarction it was 12 7 years. No matter the mode of onset, the course of coronary disease was marked by fluctuations in degree of anginal pain, with episodes of coronary insufficiency or recurrent myocardial infarction, as well as periods of well being Thirty-four of the men and all nine of the women had hypertension. Eight had diabetes Sixteen had intermittent claudication Seventeen patients suffered from heart failure at some time during the course of their heart disease. Fifty-three patients died with cases as follows: myocardial infarction, 21, sudden death, 11; heart failure, 3, cerebral vascular insult, 3; noncardiac disease, 6, and unknown, 9

Ryle and Russell (13) studied 243 cases of coronary artery disease in a period between 15 and 25 years There were 164 males and 79 females, a ratio of about 2.1. The clinical age of onset for the males varied from the youngest of 34 years to an oldest of 90 years, for the females 35 years to 83 years Of the 164 male cases, 97 (60 per cent) were primarily classified as angina pectoris and 67 (40 per cent) as coronary thrombosis. Of the 79 female cases, it was 47 (60 per cent) and 32 (40 per cent), respectively There was a family history relating to a parent, brother or sister in 12 male cases (7 per cent) and in 8 female cases (10 per cent). Hypertension of 160/100 mm Hg. or over were recorded in 66 of 150 cases (44 per cent).

James, Post and Smith (99) reviewed the case histories of 146 women

with myocardial infarction. The average age of menopause was 47.4 years and the average age of initial infarction was 16.6 years later. Hypertension and/or diabetes was present in 69.9 per cent of the entire series, 63 6 per cent of the living patients, 77.6 per cent of the fatal cases, and 90.9 per cent of the premenopausal group Therefore, only 1 patient of the premenopausal group had a myocardial infarction presumably due to spontaneous coronary arteriosclerosis, without diabetes or hypertension, and she was moderately obese These findings again emphasize the high incidence of hypertension and diabetes in women with myocardial infarction, their relative protection against myocardial infarction in the absence of hypertension and diabetes in the premenopausal state and the contrast by comparison of the proclivity for coronary atherosclerosis for men in a comparable age group

THE CLINICAL ASPECTS OF CORONARY ATHEROSCLEROTIC DISEASE

Arteriosclerotic coronary artery disease may exist without symptoms and without abnormal cardiovascular physical findings Further, the commonest complaint in symptomatic coronary arteriosclerotic disease is chest pain. It is known that 25 to 40 per cent of persons with a typical history of angina of effort have normal resting electrocardiograms and normal physical findings A problem in differential diagnosis arises because chest pain of typical effort angina may be simulated by disorders of structures of the chest besides the heart. These include myalgia of chest muscles, cervical and upper thoracic spondylitis and neuritis, pulmonary infarction and embolism, cardiospasm, esophageal hiatus hernia and others

Coronary Failure: This is defined as a state of failure of the coronary circulation, from whatever cause, which is more prolonged than angina pectoris without, however, producing acute myocardial infarction (13a) In terms of symptoms, it refers to cardiac pain lasting from one-half to many hours which usually does not respond to nitroglycerin or rest. In terms of signs and laboratory findings, it lacks the elevated fever, elevated sedimentation rate, elevated leucocytosis, change in blood pressure, progressive electrocardiographic changes, shock and pulmonary edema seen in myocardial infarction. On pathological examination, no resultant myocardial infarction or extensive myocardial fibrosis will be found and the underlying mechanism for the pain must be sought in prolonged but reversible myocardial ischemia. Freedberg *et al.* point out that the practical aspects of making a proper diagnosis lies in the nature of the medical care required—less prolonged care than myocardial infarction and more attention than angina pectoris with regard to bed rest. Since no thrombus (coronary arterial or mural) has been formed, dicumarolization or heparinization is not indicated.

Coronary Insufficiency. This name has been given to a clinical state in which no acute coronary artery occlusion takes place but in which the precipitating cause produces a degree of insufficiency of coronary flow for a sufficient time to produce focal or even diffuse subendocardial necrosis or papillary muscle necrosis The localization of the lesions in these areas is attributed to the fact that they are remote from the source of blood supply This disease may end fatally (13b).

The precipitating factors have been listed (13c, d) as: Sexual intercourse or straining at stool with excess exertion, extremes in heat or cold; tachycardia; auricular fibrillation or auricular flutter, shock; heart failure; hypoglycemia; operation; anesthesia, anoxemia of many types, carbon monoxide poisoning; acute hemorrhage; chronic anemia; pulmonary embolism; hyperthyroidism, and hypothyroidism.

Here, as in coronary failure, the signs and symptoms except for pain may be slight or absent. However, there is a characteristic electrocardiographic pattern which consists of RS-T depression and T wave inversion in one or more leads This is related to the subendocardial localization of the lesions as opposed to the usual epicardial localization in acute myocardial infarction where RS-T elevations are more common.

Freedberg (13a) holds that coronary insufficiency is really a pathologic diagnosis and even Master (13e) admits to a confusion of terms. Nevertheless, as far as cardiac pain is concerned, coronary failure or coronary insufficiency represent similar states of diminished coronary flow with resultant myocardial ischemia.

Myocardial Infarction: The clinical picture of myocardial infarction includes severe pain, fever, leucocytosis, changes in the electrocardiogram and sedimentation rate. This complication of coronary artery disease will be considered in detail later.

Chest Pain of Effort Angina: The diagnosis of effort angina of coronary artery disease origin on history alone has been possible in the classical case ever since the days of William Heberden (1768) (14, 15) The following is Heberden's description (15): . . "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris

"They who are afflicted with it, are seized while they are walking, (more especially if it be up hill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue but the moment they stand still, all this uneasiness vanishes.

with myocardial infarction. The average age of menopause was 47.4 years and the average age of initial infarction was 16.6 years later. Hypertension and/or diabetes was present in 69.9 per cent of the entire series, 63 6 per cent of the living patients, 77.6 per cent of the fatal cases, and 90.9 per cent of the premenopausal group. Therefore, only 1 patient of the premenopausal group had a myocardial infarction presumably due to spontaneous coronary arteriosclerosis, without diabetes or hypertension, and she was moderately obese. These findings again emphasize the high incidence of hypertension and diabetes in women with myocardial infarction, their relative protection against myocardial infarction in the absence of hypertension and diabetes in the premenopausal state and the contrast by comparison of the proclivity for coronary atherosclerosis for men in a comparable age group.

THE CLINICAL ASPECTS OF CORONARY ATHEROSCLEROTIC DISEASE

Arteriosclerotic coronary artery disease may exist without symptoms and without abnormal cardiovascular physical findings Further, the commonest complaint in symptomatic coronary arteriosclerotic disease is chest pain. It is known that 25 to 40 per cent of persons with a typical history of angina of effort have normal resting electrocardiograms and normal physical findings. A problem in differential diagnosis arises because chest pain of typical effort angina may be simulated by disorders of structures of the chest besides the heart. These include myalgia of chest muscles, cervical and upper thoracic spondylitis and neuritis, pulmonary infarction and embolism, cardiospasm, esophageal hiatus hernia and others

Coronary Failure: This is defined as a state of failure of the coronary circulation, from whatever cause, which is more prolonged than angina pectoris without, however, producing acute myocardial infarction (13a) In terms of symptoms, it refers to cardiac pain lasting from one-half to many hours which usually does not respond to nitroglycerin or rest. In terms of signs and laboratory findings, it lacks the elevated fever, elevated sedimentation rate, elevated leucocytosis, change in blood pressure, progressive electrocardiographic changes, shock and pulmonary edema seen in myocardial infarction. On pathological examination, no resultant myocardial infarction or extensive myocardial fibrosis will be found and the underlying mechanism for the pain must be sought in prolonged but reversible myocardial ischemia. Freedberg *et al.* point out that the practical aspects of making a proper diagnosis lies in the nature of the medical care required—less prolonged care than myocardial infarction and more attention than angina pectoris with regard to bed rest Since no thrombus (coronary arterial or mural) has been formed, dicumarolization or heparinization is not indicated.

group were found to have parallel findings so that in any individual case some symptom usually associated with true angina of effort was elicited in the functional or non-cardiac patient. There were, however, certain leading differential symptoms. In the functional cases, the pain is apt to occur as frequently at rest as on effort, in the organic cases, the pain occurs more frequently on effort than at rest. Pain induced by cold was apt to be organic

As will be described in the following pages, the problem of overlap between cardiac and non-cardiac origins of chest pain applies not only to symptomatology but also to objective testing for angina pectoris whether the tests be biochemical or graphic (18).

OBJECTIVE TESTS FOR DIAGNOSIS OF EFFORT ANGINA

Philips, Chapman and Goerke (19) investigated the relative value of certain poignant techniques in the detection of heart disease. These techniques included History, a 12 or 13-lead electrocardiogram, fluoroscopy of the chest, electrokymogram, a 70 mm minifilm of the chest, and serum cholesterol and serum lipoproteins The survey included 2,252 individuals with a mean age of 43 7 years There were 1,859 men and 393 women In the detection of coronary arteriosclerosis heart disease, physical examination and fluoroscopy were found to be insensitive. The value of the electrokymogram was also in doubt The history was the best method of detecting coronary arteriosclerotic disease and the following questions were of most value: "Do you ever have distress, pain, or an uncomfortable feeling in the chest while walking on the street or up inclines or steps", "While walking, are you forced to stop in order to rest", "have you noticed increasing or undue shortness of breath with exertion" The electrocardiogram was most sensitive in detecting hypertensive heart disease The three standard leads were practically as sensitive as 12 or 13 leads (57 per cent as compared with 65 per cent) The three questions above and the three standard leads of the electrocardiogram detected 92 per cent of all heart cases, but 35 per cent of normal individuals also either answered any one of the three questions affirmatively or had abnormalities in the three standard lead electrocardiogram No significant difference was found between the mean levels of S_f 12-20 lipoproteins in those with heart disease as compared to those without heart disease.

Rinzler (18) also indicated that the limitations of the serum lipoproteins as a diagnostic test in angina is due to the fact that even in definite coronary insufficiency these lipoproteins of the S_f 10-20 class may vary from the limit of resolution (less that 5 mg per cent) to over 80 mg per cent The test indicates the presence of atherosclerotic activity but does not specifically indicate disease of the coronary arteries sufficient to cause angina pectoris The serum lipoprotein levels listed in Table 7, demonstrates the wide range of S_f 12-20 levels in patients with proved angina pectoris.

"In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different The pain is sometimes situated in the upper part, sometimes in the middle, *sometimes at the bottom of the os sterni, and often* more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm Males are most liable to that disease, especially such as have past their fiftieth year.

"After it has continued a year or more, it will not come so instantaneously upon standing still, and it will come on not only when the persons are walking, but when they are lying down, especially if they lie on their left side, and oblige them to rise up out of their beds In some inveterate cases it has been brought on by the motion of a horse, or a carriage, and even by swallowing, coughing, going to stool, or speaking, or any disturbance of mind

"Such is the most usual appearance of this disease, but some varieties may be met with Some have been seized while they were standing still or sitting, also upon first waking out of sleep, and the pain sometimes reaches to the right arm, as well as to the left, and even down to the hands, but this is uncommon in a very few instances the arm has at the same time been numbed and swelled In one or two persons the pain has lasted *some hours, or even days, but this has happened when the complaint* has been of long standing, and thoroughly rooted in the constitution once only the very first attack continued the whole night"

With about a 200-year span in between, compare Heberden's description of classical angina pectoris with Zoll, Wessler and Blumgart's (16) words. "We accept the term angina pectoris to denote a syndrome of paroxysmal substernal or precordial pain or discomfort of short duration, frequently radiating to the shoulders and inner aspects of the arms, precipitated by *exertion, emotion, or other states in which* the work of the heart is increased, and relieved by rest or nitroglycerin."

It would certainly appear from these apt descriptions that the diagnosis of effort angina could be made from the history alone. Master, Jaffe and Pordy (17), however, analyzed the chest pain of 100 patients with angina pectoris and abnormal resting electrocardiograms and of 100 non-cardiac or functional patients with negative resting electrocardiograms. The following components of chest pain were evaluated Duration of each attack; frequency of attacks, type (pressure, constriction, aching, tightness, choking, sticking, burning), location (substernal, precordial, entire chest, left chest, right chest, back epigastrium); radiation, onset (effort, emotional, spontaneous, meals, cold, intercourse), and relief (nitroglycerin, rest, whiskey, belching, spontaneous). Patients in both the cardiac and non-cardiac

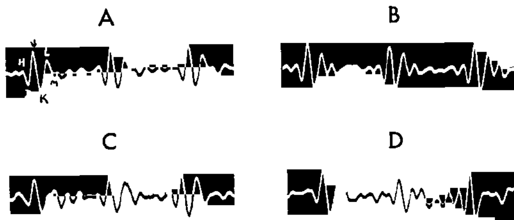


Fig. 18. The normal ballistocardiogram (32-year-old white male). (A) Breath held in mid respiration with forcing. (B) Graph taken at deep inspiration with breath held. (C) Graph taken at deep expiration with breath held. (D) Graph taken with patient respiring quietly but freely (Dock electromagnetic instrument)

Riseman and Josephs (21) found that the 12-lead electrocardiogram gave more information of value in angina pectoris than could be obtained from the three standard leads plus one apical lead Odle, Wechsler and Silverberg (22) indicated that even when the 12-lead electrocardiogram was normal, electrocardiographic leads demonstrating the left ventricular cavity may give specific objective evidence of coronary insufficiency In this method the exploring electrode is placed in the left supraclavicular fossa over the clavicle at the lateral border of the sternocleidomastoid muscle. In 5 out of 100 patients in whom such electrocardiograms were taken, changes were demonstrated in the left ventricular cavity leads but in none of the other leads The normal pattern is a QS and inverted T. In abnormal patterns either the upright T waves elevation of the S-T segment, appearance of a prominent R wave, or combination of the latter occurred These 5 patients had clinical evidence of angina pectoris and yet showed no electrocardiographic abnormalities by standard and unipolar limb and precordial leads

There are certain circumstances where despite a typical history of angina pectoris, the physician needs or wants confirmatory objective findings of coronary artery disease. The insurance medical examiner (23) needs more than the history to prove either freedom from angina in an applicant for a policy, or of the presence of coronary arteriosclerotic disease in a claimant for disability The industrial physician also needs objective data on the employee in compensation questions The practicing physician may want confirmatory evidence before giving his patient practical advice for the future The relative value of the electrocardiogram, the ballistocardiogram, stress tests, the level of serum lipoproteins molecules and the ratio of phos-

TABLE 7

CLINICAL DATA, SERUM LIPOPROTEIN LEVELS, AND ATHEROGENIC INDICES IN PATIENTS WITH EFFORT ANGINA AND ARTERIOSLEROTIC HEART DISEASE

No.	Age	Sex	Serum Lipoprotein Levels (taken Feb., March, 1952) Sf 0-12 mg %	Sf 12-20 mg %	Sf 20-100 mg %	Sf 12-400 mg %	Atherogenic Index	Old Myocardial Infarction	Serum Lipoprotein Levels (taken Dec. 1955) Sf 0-12 mg. %	Sf 12-400 mg %	Atherogenic Index	Remarks
1.	47	M	365	18	65	154	64	No	561	129	79	Alive 1956
2.	61	M	365	22	46	144	62	Yes	465	51	55	Alive 1956
3.	58	M	421	18	57	139	66	Yes				Alive 1956
4.	79	M	273	11	12	106	46	Yes				Alive 1956
5	67	M	338	20	113	238	75	Yes				Alive 1956
6	59	M	472	106	247	605	153	Yes				Alive 1956
7	58	F	408	40	69	251	85	Yes	427	504	131	Alive 1956
8	74	M	390	32	33	130	62	No	543	260	100	Alive 1956
9	68	M	370	18	95	164	66	No				Alive 1956
10.	52	M	293	34	114	240	71	Yes				Died Jan. 1956
11.	66	M	408	30	96	224	80	No				Alive 1956
12.	53	M	452	43	89	251	89	No				Alive 1956
13.	76	M	468	44	110	266	91	Yes				Alive 1956
14.	75	M	370	18	10	89	53	No				Alive 1956
15.	59	M	423	30	79	246	86	Yes				Died July 2, 1955
16.	52	F	576	102	273	666	174	Yes				Alive 1956
17	76	M	452	73	135	387	113	Yes				Died 1955
18	70	M	421	16	48	139	66	No				Alive 1956

indirect instruments were classified as high frequency (26) and low frequency (28).

Many types of direct instruments were used, namely, the electromagnetic (27, 30-33), the photo-electric (34), the piezo-electric (35) and combinations of electromagnetic and photo-electric. The internally impressed force derived from the cardiac propulsive effort was described in terms of its principle functions, namely, displacement, velocity, and acceleration and an instrument was described to measure all three (36-38).

By whatever direct instrument one records the ballistogram, the normal



Fig. 20. The ballistocardiogram of a 52-year-old white male with a history of effort angina, a normal resting electrocardiogram and a positive Master 2-step test. It shows an "M" shaped component beginning at the height of the J wave during ballistocardiographic systole (Dock electromagnetic instrument).

curve is represented by: (1) regularity of the pattern from beat to beat, and (2) definitiveness, that is, the ability to distinguish at a glance the various waves in the complex (Fig 18). In general, the abnormal patterns are represented as follows (39-49).

1 The H-wave amplitude may be equal or higher than the J-wave.
2 The I-wave may disappear.
3. The J-wave becomes "M" shaped at its peak (late "M" type of Starr).
4. The J-wave occurs late in systole giving a deep K (late downstroke type).
5 The L and after-waves may be accentuated
6 There may be upward bowing of the J-K segment

Brown *et al* (29) besides studying the complex itself, analyzed the degree of variation between inspiration and expiration which they called the respiratory variation index (RVI) with the following formula:

$$\text{RVI} = \frac{\text{(largest inspiratory minute volume)} \quad \text{minus} \quad \text{(smallest expiratory minute volume)}}{\text{Surface area}}$$

The normals were found to have an RVI between 0 and 450 cc. per minute per square meter of body surface axis. Any variation above 450 cc.

pholipid to serum cholesterol will be discussed as objective tests for the determination of whether chest pain is of coronary artery origin (18).

THE BALLISTOCARDIOGRAM IN CORONARY ARTERY DISEASE

In 1947 and later, Starr (24, 25) reviewed the 8 to 10-year after-histories of 90 persons over 40 years of age on whom ballistocardiograms had been taken. Four of the subjects had had abnormal ballistocardiograms 8 to 10 years previously. Three of the 4 developed coronary artery disease in the years which followed. Five subjects with normal ballistocardiograms in 1937, 1938, and 1939, died within the next 8 to 10 years. None developed clinical evidence of heart disease, and in 2 the heart was normal at necropsy. Starr indicated on the basis of these findings that abnormal ballistocardiograph might presage and predict future heart disease (26).

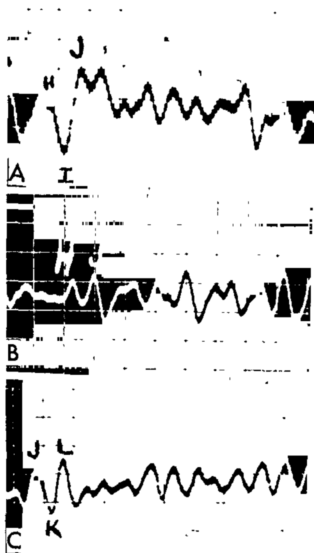


Fig 19 Abnormal ballistocardiogram (A) This demonstrates the abnormality in the J wave which is notched at its peak (late "M" type) (B) The early "M" type The H and J waves are about equal in height (C) The late "M" type The J and L are of about equal height and the K is shallow (Dock electromagnetic instrument)

In 1949, Dock and Taubman (27) described a small, inexpensive electromagnetic ballistocardiogram readily usable in office work for recording the ballistocardiogram directly from the body. The curves obtained with the electromagnetic instrument compared so well with those obtained with the more expensive instruments (26, 28, 29) which record the velocity of bodily motion rather than the distance moved by the body that, to all intents and purposes, the clinical significance was the same. The

abnormal in 70 (93 per cent) of 75 patients with angina pectoris, normal resting electrocardiograms, and positive two-step tests They also found that 27 (23 per cent) of 113 patients with negative two-step electrocardiographic tests had abnormal ballistocardiograms at rest or after exercise. This means that in 156 (83 per cent) of 188 patients, there was a direct correlation between positive ballistocardiograms and positive exercise tolerance tests and between negative ballistocardiograms and negative exercise tolerance tests A high percentage of such correlation was also found by Rinzler, Bakst and Rosenfeld (32).

According to Scarborough (50) (Fig. 21), 10 per cent of the clinically normal population have abnormal ballistocardiograms in the fifth decade, 33 per cent in the sixth decade, 69 per cent in the seventh decade and 92 per cent in the eighth decade At the same time, the incidence of abnormal electrocardiograms are rising from 2 per cent to only 8 per cent through these decades in the clinically normal population These findings led Scarborough and his associates to conclude that abnormal ballistocardiograms below the age of 40 or normal ballistocardiograms above the age of 60 should be looked upon with significance If the ballistocardiographic interpretation coincides with the other laboratory data, then it may be given weight On the other hand, if the ballistocardiogram is abnormal in the absence of other confirmatory findings, one should reserve opinion as to its clinical significance

Dock and Mandelbaum (40) believe that poor physical condition and especially the flabby abdominal muscles which give sedentary men potbellies, account for some of the Grade 1 traces, and that these factors plus emphysema account for some of the Grade 2 traces in older people They feel that the ballistocardiograph appears to be sensitive, but not a specific tool for case findings in latent coronary disease

STRESS TESTS FOR USE IN PATIENTS WITH CHEST PAIN AND NORMAL RESTING ELECTROCARDIOGRAMS

Exercise Tests: There are several types of exercise tests now in use Barker (23) states that in older persons (50 years or over) who have typical symptoms of angina pectoris, it is often not necessary to make a record during an attack of angina pectoris. However, in the following types of patients, as listed by Barker (23),* this may be very important

A. Patients below 50 years of age, especially those below 40 years. When symptoms are typical and an adequate cause cannot be found to explain them, or if there are typical symptoms and the resting electrocardiogram is not outside normal limits or displays only minor deviations, there should

* From Barker, J M *The Unipolar Electrocardiogram* Courtesy of Appleton-Century-Crofts, Inc

was considered abnormal. They use the following arbitrary grades of abnormality to classify the ballistocardiogram (Figs. 19 and 20):

0 = normal tracing

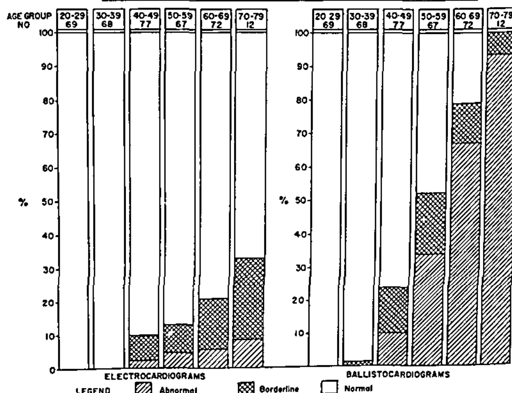
Grade 1: The regularity and definitiveness are preserved. The inspiratory IJ amplitude is normal. The expiratory complexes, however, are decreased in amplitude.

Grade 2. One-half or more of the complexes are abnormal, again mainly during expiration.

Grade 3: The complexes in both inspiration and expiration show varying degrees of abnormality and definitiveness The complexes are still individually identifiable. The amplitude of all the complexes is low.

Grade 4: Totally abnormal complexes are present throughout. They are of low amplitude, unidentifiable, and irregular.

Taymor and his co-workers (34) found that the ballistocardiogram was



of 40, the frequency of abnormal electrocardiograms increases gradually to a maximum of 8 per cent, abnormal ballistocardiograms increase precipitously to a maximum of 92 per cent (Courtesy of Dr. W R. Scarborough and *American Heart Journal* (50).)

interval is taken as the control level. Depression of the RS-T segment of over 0 5 mm in any lead is considered a positive result. A change from an upright T to an isoelectric (flat) or inverted T-wave is also an abnormal response (Fig. 22B); so, too, is a change in the other direction, that is, from a flat or negative to a positive T-wave. Occasionally, premature beats or some significant arrhythmia, widening of the QRS, intraventricular or bundle branch, large Q waves, prolongation of the P-R interval, or heart block may appear. All of these are abnormal responses to the exercise A change from an inverted or flat T-wave to an upright T-wave is abnormal A change from an inverted T-wave to an upright wave in lead III alone is not a positive result. Elevated S-T segments which return to base line after exercise are not abnormal.

TABLE 8

Two-step Trips for Standard Tests

Weight					*Age*						
(lb)	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*
					Males						
50-59	32										
60-69	31										
70-79	30										
80-89	29	29	29	28	27	27	26	25	25	24	23
90-99	28	28	28	27	27	26	25	25	24	23	22
100-109	27	28	28	27	26	25	25	24	23	22	22
110-119	26	27	27	26	25	25	24	23	23	22	21
120-129	25	26	27	26	25	24	23	23	22	21	20
130-139	24	25	26	25	24	23	23	22	21	20	20
140-149	23	24	25	24	24	23	22	21	20	20	19
150-159	22	24	25	24	23	22	21	20	20	19	18
160-169	21	23	24	23	22	22	21	20	19	18	18
170-179	20	22	23	23	22	21	20	19	18	18	17
180-189	19	21	23	22	21	20	19	19	18	17	16
190-199	18	20	22	21	21	20	19	18	17	16	15
200-209		19	21	21	20	19	18	17	16	16	15
210-219		18	21	20	19	18	17	17	16	15	14
220-229		17	20	20	19	18	17	16	15	14	13
					Females						
50-59	32										
60-69	30										
70-79	29										
80 89	28	28	28	27	26	24	23	22	21	21	20
90-99	26	27	26	25	24	23	22	22	21	20	19
100-109	25	26	26	25	24	23	22	21	20	19	18
110-109	23	25	25	24	23	22	21	20	19	18	18
120-129	22	24	24	23	22	21	20	19	19	18	17
130-139	20	23	23	22	21	20	19	19	18	17	16
140-149	19	22	22	21	20	19	19	18	17	16	16
150-159	17	21	20	20	19	19	18	17	16	16	15
160-169	16	20	19	19	18	18	17	16	16	15	14
170-179	14	19	18	18	17	17	16	16	15	14	13
180-189	13	18	17	17	17	16	16	15	14	14	13
190-199	12	17	16	16	16	15	15	14	13	13	12
200-209		16	15	15	15	14	14	13	13	12	11
210-219		15	14	14	14	13	13	13	12	11	11
220-229		14	13	13	13	13	12	12	11	11	10

Courtesy Dr Arthur M Master and *American Heart Journal* (24 777, 1942).

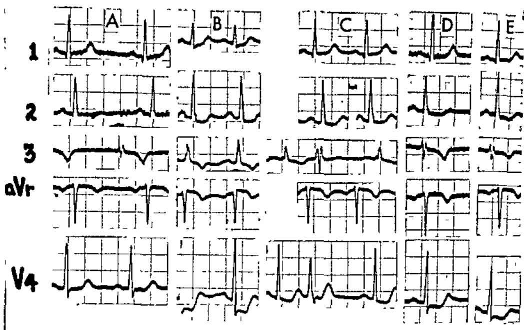


Fig 22 Electrocardiograms taken on a patient with coronary artery disease, effort angina and a normal resting electrocardiogram to demonstrate a positive stress test with exercise, ergonovine and anoxemia (A) Control electrocardiogram (B) Electrocardiogram immediately after exercise Note S-T segment depressions (C) Fifteen minutes after exercise The S-T segments have returned toward the iso-electric level (D) Ten minutes after the intravenous administration of 0 2 mg of ergonovine maleate Note S-T segment depression in leads II and V_4 (E) A positive anoxemia test as shown by S-T segment depression in leads II and V_4 in the electrocardiogram taken 20 minutes after the start of the anoxemia test (Courtesy of Dr Isidore Stein and *New York State Journal of Medicine* (66))

be an objective record. It is most unfair to "tag" an individual with the diagnosis of angina pectoris or coronary artery disease who does not have it The resulting anxiety state may be worse than the organic disease.

B Any patient at any age displaying typical or atypical symptoms but whose resting electrocardiogram is not abnormal and in whose case one or more of the following is in question

1 Insurance liability
2 Insurance benefits
3. Military service
4 Litigation of various sorts.
5. Individuals in responsible or "key positions" If it is impossible for the physician to make a tracing at the time that there is a spontaneous attack, and an attack should be induced by exercise.

1. The Two-step Exercise Electrocardiogram (Master Test (51)) This consists of ascending and descending two 9-inch steps (22 to 27 inches wide) a variable number of times (depending on age and weight) in 1½ minutes (Table 8). In interpretation of the electrocardiogram, the P-R

tive under these conditions and if the clinician is convinced of the necessity of a further test, the amount of exercise may be cautiously increased.

One must be especially careful to register and interpret the electrocardiogram immediately before the test in order to detect an acute infarction that may have developed between the clinical examination and the test. Tracings should be done before, immediately after, and 2, 5, and 10 minutes after the exercise

Any definite widening of the QRS complex after exercise is pathologic. S-T depressions between 1.5 to 2 mm. are probably abnormal. If it is less than 1.5 mm., it is a normal test Any shift of the T vector after exercise to the extent that a distinctly inverted T in any or all of leads I, II, V_4, V_5 and V_6 is inscribed, is definitely pathologic. However, reversal of T waves in leads that are near the transitional zone of the normal T vector are not to be interpreted as abnormal If the T becomes lower or inverted at a time when the tachycardia after exercise is diminishing, then its pathologic significance is enhanced. A reversal of the U waves after exercise is definitely abnormal; so is the appearance of extrasystoles or paroxysmal arrhythmias.

3. Littman and Rodman Test (54) This exercise test is a variation of the Master Two-step test in that patients walk over two 9-inch steps Where the history indicates that the complaint is more commonly experienced at some particular hour of the day, the test is performed at that time. If no such temporal factor is elicited, the test is always run in midafternoon following a medium or large noon meal. In order to produce a constant and easily reproducible cold stimulus (as suggested by Riseman, Waller and Brown), the patient performs the exercise while holding in each hand approximately 4 ounces of gauze wrapped ice The exercise is carried out at the patient's own rate except when this proves to be unusually slow or fast Under these circumstances, a metronome adjusted to sound 60 beats to the minute is employed to regulate the pace. The patient is instructed to take one step at each beat and allow 2 beats for turning A complete single trip can thus be made in 6 seconds· 2 seconds up, 2 seconds down, 2 seconds for the turn The patient is instructed to turn in opposite directions alternately to minimize the tendency to vertigo The subjects walks over the steps until he experiences pain or until he is forced to stop by dyspnea or fatigue. Failing this, the trip is continued until 100 single or 50 round trips have been completed

A six lead record consisting of leads I, II, III, V_4 and V_5 is made before beginning and upon completion of the test. The limb lead electrodes are left on during the exercise so that it is possible to make the second electrocardiogram immediately This is not ordinarily done, however, until the pulse rate has slowed to 100 per minute or less

Positive tests consist of extensive S-T depressions, T-wave reversions, or

The procedure for obtaining electrocardiographic records in the "two-step" test is as follows: The electrodes are attached to the patient and his weight is recorded. He is then requested to sit down in a reclining chair or to lie on the examination table and to make himself comfortable. The number of times that he is to climb the "steps" is determined from the standard table (Table 8). Next the electrocardiogram is taken. The technician or physician then demonstrates the procedure by climbing over the steps two or three times The patient, at a given command walks up one side of the steps and down the other, always turning to the same wall or side of the room before each ascent to prevent vertigo. He makes a trip only when he receives the count and the required number of ascents is completed in 1½ minutes. If the patient climbs too slowly, he is told to move more rapidly, if too fast, his ascents are made more deliberate. A stop watch, a wrist watch or electric clock with a sweep hand is used. At cessation of the exercise, the patient sits down and the four leads of the electrocardiogram are recorded immediately. The electrocardiogram is then recorded at 2 and 6 minutes after cessation of exercise Only a few beats in each lead are necessary Placing the steps near or against a wall gives a patient a sense of security Further reassurance may be afforded by holding the patient's arm and guiding him over the steps, providing the examiner exerts no vertical lift.

If the single "two-step" test just described is negative, the test should be repeated at another time with twice the standard amount of work in 3 minutes (double "two-step" test)

2. Scherf Test (52, 53). In 1932, Goldhammer and Scherf found electrocardiographic changes in 11 of 20 patients with angina pectoris after exercise In 1933, they recommended an exercise test to determine the adequacy of the coronary circulation for the early diagnosis of angina pectoris

Scherf believes that the actual form of exercise is unimportant. Stair-climbing, knee-bending, sitting-up exercises, and raising dumbbells may be used From the patient's story, one determines the amount of exertion needed to bring on symptoms and also the amount which the patient permits himself to perform daily The exercise prescribed for the test does not exceed the latter and approximates the former. Patients who develop pain only after severe exertion are asked to climb several flights of stairs rapidly. Those who experience pain after mild exertion are asked to climb one flight. Those who develop pain after the slightest exertion are asked to bend the knees a few times or sit up in bed several times If the patient states that the pain appears only on exertion following a heavy meal, the test is done after such a meal In order to avoid an excessive degree of ischemia of the heart muscle, the first test is always limited to the amount of work which the patient does spontaneously during his daily routine. If the test is nega-

tive under these conditions and if the clinician is convinced of the necessity of a further test, the amount of exercise may be cautiously increased.

One must be especially careful to register and interpret the electrocardiogram immediately before the test in order to detect an acute infarction that may have developed between the clinical examination and the test. Tracings should be done before, immediately after, and 2, 5, and 10 minutes after the exercise

Any definite widening of the QRS complex after exercise is pathologic. S-T depressions between 1.5 to 2 mm. are probably abnormal If it is less than 1 5 mm, it is a normal test. Any shift of the T vector after exercise to the extent that a distinctly inverted T in any or all of leads I, II, V_4, V_5 and V_6 is inscribed, is definitely pathologic However, reversal of T waves in leads that are near the transitional zone of the normal T vector are not to be interpreted as abnormal. If the T becomes lower or inverted at a time when the tachycardia after exercise is diminishing, then its pathologic significance is enhanced. A reversal of the U waves after exercise is definitely abnormal; so is the appearance of extrasystoles or paroxysmal arrhythmias.

3. **Littman and Rodman Test** (54) This exercise test is a variation of the Master Two-step test in that patients walk over two 9-inch steps. Where the history indicates that the complaint is more commonly experienced at some particular hour of the day, the test is performed at that time If no such temporal factor is elicited, the test is always run in midafternoon following a medium or large noon meal In order to produce a constant and easily reproducible cold stimulus (as suggested by Riseman, Waller and Brown), the patient performs the exercise while holding in each hand approximately 4 ounces of gauze wrapped ice. The exercise is carried out at the patient's own rate except when this proves to be unusually slow or fast. Under these circumstances, a metronome adjusted to sound 60 beats to the minute is employed to regulate the pace. The patient is instructed to take one step at each beat and allow 2 beats for turning A complete single trip can thus be made in 6 seconds 2 seconds up, 2 seconds down, 2 seconds for the turn The patient is instructed to turn in opposite directions alternately to minimize the tendency to vertigo The subjects walks over the steps until he experiences pain or until he is forced to stop by dyspnea or fatigue Failing this, the trip is continued until 100 single or 50 round trips have been completed.

A six lead record consisting of leads I, II, III, V_4 and V_5 is made before beginning and upon completion of the test The limb lead electrodes are left on during the exercise so that it is possible to make the second electrocardiogram immediately This is not ordinarily done, however, until the pulse rate has slowed to 100 per minute or less.

Positive tests consist of extensive S-T depressions, T-wave reversions, or

The procedure for obtaining electrocardiographic records in the "two-step" test is as follows: The electrodes are attached to the patient and his weight is recorded. He is then requested to sit down in a reclining chair or to lie on the examination table and to make himself comfortable. The number of times that he is to climb the "steps" is determined from the standard table (Table 8). Next the electrocardiogram is taken. The technician or physician then demonstrates the procedure by climbing over the steps two or three times The patient, at a given command walks up one side of the steps and down the other, always turning to the same wall or side of the room before each ascent to prevent vertigo. He makes a trip only when he receives the count and the required number of ascents is completed in 1½ minutes If the patient climbs too slowly, he is told to move more rapidly; if too fast, his ascents are made more deliberate. A stop watch, a wrist watch or electric clock with a sweep hand is used. At cessation of the exercise, the patient sits down and the four leads of the electrocardiogram are recorded immediately. The electrocardiogram is then recorded at 2 and 6 minutes after cessation of exercise Only a few beats in each lead are necessary Placing the steps near or against a wall gives a patient a sense of security Further reassurance may be afforded by holding the patient's arm and guiding him over the steps, providing the examiner exerts no vertical lift

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reached the top, or before if he became distressed on the way, he was hurried down again and immediately reconnected to the electrocardiograph.

Positive results consisted of horizontal depression or sagging of the RS-T segment of 1 to 4 mm., a completely flat T wave, a diphasic T wave, the first part of which was negative, or actual inversion of the T wave.

Evaluation of Exercise Tests Master and Chesky (57) followed-up 300 patients seen consecutively in private practice beginning in 1946 These patients all had normal resting 12-lead electrocardiograms and the majority complained of chest pains. The patients were divided into two equal groups The first group consisted of 150 patients with both negative single and double Master two-step exercise tests. The second group consisted of 150 patients in whom either the single or double two-step test exercise electrocardiogram was positive. The average follow-up period extended for from 3 to 4 years.

Among the group of 150 patients with negative single and double Master two-step exercise tests, only 1 woman sustained a coronary occlusion 3 years later, no other instance of spontaneous coronary disease occurred Among the group of 150 patients with positive single or double Master two-step exercise tests, 86 patients (nearly 60 per cent) had spontaneous attacks of coronary occlusion or insufficiency either before or after the exercise test was found to be positive Twelve deaths occurred among these patients, 10 as a result of coronary occlusion. Of the remaining 64 cases, 49 had definite clinical coronary artery disease However, it is to be remembered that coronary insufficiency may occur either on a functional or an organic basis Thus, in the remaining 15 persons in this latter group, the clinical impression that the heart disturbance was functional, was confirmed by a normalization of the positive exercise tests, following the administration of dyhydroergocornine (51)

Positive results with exercise tests vary from 52 to 88 per cent (52, 53, 56, 59), according to the technic and especially with the degree of exercise As for false positive, the Master group (60) found that 2 5 per cent of 200 normal persons had positive single "two-step" tests, and 6 5 per cent had either positive single or double "two-step" tests or both This is in contrast to the findings of Davis *et al* (61) who found the electrocardiographic exercise test of the Master type to be positive in 22 8 per cent of the normal controls Normal women showed a far higher incidence of positive tests than did the men, actually 45 5 per cent of the normal women had positive tests, as contrasted to 13 6 per cent of the control men There was no definite age trend in the normal group.

STRESS TESTS WITH DRUGS

Stein Ergonovine Test (62-66). The present test is carried out as follows: At each test, the exact location of pain induced by effort is noted A control

both In all instances, these may be seen in more than one lead, particularly in the precordial position.

4. Glyceryl Trinitrate-Exercise Test: Under conditions individually standardized for each subject, referable to emotional state, meals, time of day, and so on, exercise consisting of climbing stairs at a constant rate (number of steps climbed a minute) is performed before and after the sublingual administration of glyceryl trinitrate (55). The climbing may be done on a "two-step box" or a convenient flight of stairs. The exercise should be continued each time until minimal pain is noted in the chest or arms and then immediately discontinued. The test should be terminated before undue dyspnea or fatigue occurs The patient should be carefully instructed regarding the importance of the factor of minimal pain as an "end point" to the test. The control level of exercise tolerance should be determined by at least three separate tests, preferably with the use of sublingually administered placebos to exclude the factor of suggestion Soluble saccherin tablets are readily available and satisfactory placebos. The interval between tests should be at least 30 minutes in order to minimize the known phenomenon of increased coronary flow resulting from the initial exercise and should preferably be done on different days An increased tolerance to the exercise following administration of glyceryl trinitrate should be verified on repeated tests A schedule which has been found to be reliable follows:

Test	*Day*	*Time, Min*	*Drug*	*Steps*	*Time*
1	1	0	0	X	X
2	2	60	Placebo	X	X
3	3	120	Glyceryl Trinitrate	X	X
4	2	0	Glyceryl Trinitrate	X	X
5	2	60	Placebo	X	X
6	2	120	0	X	X

An evaluation of exercise performed under each condition should make a positive decision as to the effect of glyceryl trinitrate. The test is considered positive only if a significant increase in the exercise performance is noted after administration of glyceryl trinitrate. A positive test is considered strong evidence for a diagnosis of angina pectoris

This test devised by Reeves and Harrison (55) has as its main feature the reproduction by the test of the usual spontaneous pain, a symptom reproduced very admirably in relation to location, intensity and quality by intravenous ergonovine (vide infra).

5. Wood Test (56) The test consists of continuous effort until the patient is pulled up by pain, dyspnea or fatigue Actually this consisted of climbing 84 steps rapidly, at a moderate speed or slowly, according to the ease with which angina was said to be provoked by effort. As soon as the patient

test becomes positive, a sublingual dose of nitroglycerin (0.6 mg.) is administered to terminate pain and/or electrocardiographic changes (Figs 22D, 23).

The criteria for a positive test are one or more of the following.

1. A depression of the S-T segment of 0.75 mm. in a limb lead and 1.50 mm. in a chest lead.
2. Significant T-wave alterations in I, II or V_4
3. The development of numerous premature contractions.
4. The occurrence of pain.
5. On occasion, just as with spontaneous angina pectoris, (67, 68, 80) a transient elevation of the S-T segment instead of depression may occur after ergonovine administration (Fig 24). Sublingual nitroglycerin restores the elevation quickly to normal (69).
6. The appearance of an inverted "U" wave where one had not been present in the control and which disappears with the waning of the state of insufficiency

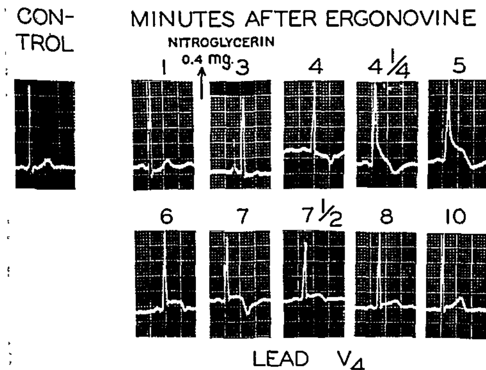


Fig. 24 Ergonovine test on a patient with the typical pain of coronary insufficiency and a normal resting electrocardiogram, who, on administration of ergonovine, developed an elevation of the S-T segment The nitroglycerin was given 1 minute after administration of the ergonovine because of the onset of drug-induced chest pain and the depression of the S-T segment (courtesy of Dr Isidore Stein).

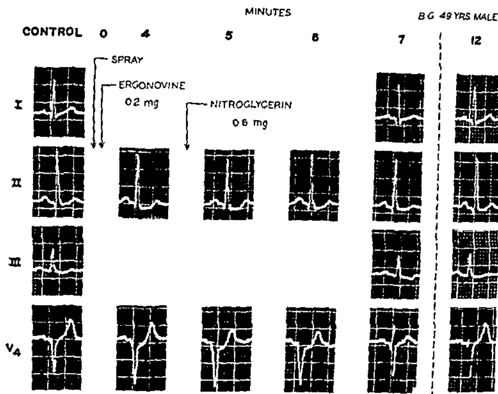


Fig 23 A positive ergonovine test in a 49-year-old male with arteriosclerotic heart disease, effort angina, and a normal resting electrocardiogram. Spray administered before the injection of 0.2 mg. of ergonovine maleate intravenously diminished but did not entirely prevent the usual chest pain occurring with administration of ergonovine alone. Note the depression of the S-T segment in lead II and V_4 4 minutes after injection. Nitroglycerin, 0 6 mg, was given immediately after this change was noted The patient was entirely comfortable throughout the test.

blood pressure, pulse rate, and resting electrocardiogram is taken Leads I, II, III, V_r and lead V_4 are recorded. The area of usual spontaneous pain is then sprayed with ethyl chloride (64, 65) or another volatile cooling agent (*fluoromethanes*). *The jet stream is swept slowly over the pain area* in one direction; timing is such that one sweep lasts about 5 seconds with a 5-second break between sweeps Since successive sweeps are applied to adjacent skin areas, any particular region is usually covered by the spray only once or perhaps twice The skin is not frosted.

After the last sweep, while lead V_4 alone or lead II and V_4 (if a direct-writing 2-channel viso-cardiette is available) are being recorded, a colorless solution containing *U S P. ergonovine maleate, 0.2 mg. per ml* of distilled water, is injected intravenously at the rate of 1 ml. per minute. The injection is stopped when either pain or electrocardiographic changes appear. Leads I, II, III, aVr and V_4 are repeated again and blood pressure is determined at 1, 5, and 10 minutes after the end of the injection. When the

test becomes positive, a sublingual dose of nitroglycerin (0 6 mg.) is administered to terminate pain and/or electrocardiographic changes (Figs. 22D, 23).

The criteria for a positive test are one or more of the following:

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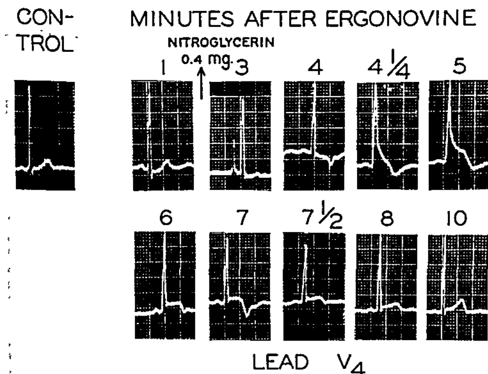


Fig 24. Ergonovine test on a patient with the typical pain of coronary insufficiency and a normal resting electrocardiogram, who, on administration of ergonovine, developed an elevation of the S-T segment. The nitroglycerin was given 1 minute after administration of the ergonovine because of the onset of drug induced chest pain and the depression of the S-T segment (courtesy of Dr. Isidore Stein).

In 76 patients with a typical history of angina of effort, 62 (82 per cent) gave a positive ergonovine test. No false positive tests occur, that is, none but patients with typical angina give a positive test. The prior spraying serves either to eliminate or decrease the intensity of pain which is usually found in 95 per cent of coronary patients given ergonovine without spray.

The advantages of this test are given as.

1 It eliminates the associated pain in a large proportion of patients.
2 Tachycardia does not usually occur to confuse the electrocardiographic interpretation
3 The test can be done on the group of patients who for reasons other than cardiac cannot exercise.
4 The positive electrocardiographic changes may be quickly reversed to normal by nitroglycerin.

Pitressin Test (70): A control electrocardiogram is taken. Pitressin in doses of 0.75 cc (15 pressor units) intravenously or 2 cc. intramuscularly, is given. The electrocardiograms are repeated. The criteria of a positive test are given as a change of a positive T, T_2 or T_4 to a flat, diphatic, or negative T wave, or S-T segment deviations totalling 3 mm. or more in leads I, II, III and IV F.

The author comments that the side-effects of pitressin renders its general use as a test for latent coronary insufficiency inadvisable.

Epinephrine Test (71): The patient is placed at rest in the recumbent position for 30 minutes or longer before observations are begun After the systolic blood pressure has reached a constant level as determined by four or five consecutive readings, a control electrocardiogram is taken Then, after again recording the blood pressure, one cc of epinephrine is injected subcutaneously. Determinations of the blood pressure are made at intervals of 2 or 3 minutes for the first hour and at 5-minute intervals for the remainder Electrocardiograms are taken at frequent intervals Observations of the blood pressure are taken until it has returned to its resting level. If at this time, the electrocardiogram still shows changes from the control traching, additional records are taken at intervals of several hours.

The T wave in the original patient increased slightly in amplitude. Normal subjects showed a tendency to decrease Typical chest pain occurs only in the anginal group This test is not in use today.

ANOXEMIA TEST

The Levy anoxemia test (72) is based on the inhalation of a mixture of 10 per cent oxygen and 90 per cent nitrogen that is passed through water. Flutter valves are incorporated in the apparatus so that rebreathing is avoided. A tank of 100 per cent oxygen is incorporated in the circuit so that oxygen can be administered quickly if needed In the routine anoxemia test, a resting electrocardiogram is made as a control Tracings are taken at

5-minute intervals during inhalation of the 10 per cent oxygen-nitrogen mixture, then 1 minute after inhalation of 100 per cent oxygen and again 5 minutes after breathing room air. The test lasts for 20 minutes unless pain ensues The tests are immediately stopped and 100 per cent oxygen administered.

The criteria for a positive test are (Fig 22E):

1. The sum of the RS-T deviations in leads 1, 2, 3 and 4F should be greater by 3 mm. or more than in the control tracings.
2. Partial or complete reversal of the direction of the T wave in lead 1, *accompanied by RS-T deviation of 1 mm or more in this lead, and*
3. Complete reversal of the direction of the T wave in lead 4F regardless of any associated RS-T deviations in this lead.

Roehm *et al* (73) have modified the test to the extent of using the Q-T_c duration before the test and 20 minutes after the test, and 2½ minutes after breathing 100 per cent oxygen They found that initial Q-T_c durations were significantly higher in patients with angina pectoris as a group than in controls. The value for the upper limit of normal is 0 480 seconds. The Q-T Anoxemia Index is calculated by adding 2 6 times the maximal increase of Q-T_c during anoxia to the Q-T_c duration (0.480 sec = (initial Q-T_c) + 2 6 (maximal increase in Q-T_c)

Tewell and Pritchard (74) and Penneys (75) have used the Millikan Oximeter to control the degree of hypoxemia. Desaturation is introduced in gradations of 5 per cent every few minutes until 70 per cent is reached Electrocardiograms are taken with each change. The test is stopped at the appearance of the first abnormal electrocardiogram

The percentage of cases of true angina pectoris failing to exhibit a positive Levy test has been variously estimated to range from 45 to 70 per cent (72, 76, 77) while false positives occur in 1 to 5 per cent of the cases (76, 77, 78, 78a)

Burnett (78b) found an incidence of 19 2 per cent false positives and concluded that the induced anoxemia test was not a dependable means of demonstrating coronary artery disease, but this work was criticized on the grounds that the study was carried out in the high altitudes of Denver, Colorado, where a 10 per cent oxygen mixture is equivalent to 8 per cent at sea level

Roehm (73) has indicated that alteration of Q-T_c duration during the course of the anoxemia test may be an additional aid in distinguishing a normal from an abnormal response since 98 5 per cent of patients considered to have true angina pectoris exhibited positive tests by the Q-T anoxemia index criterion, in contrast to only 55 2 per cent positive by the Levy criteria, while the incidence of false positives was not significantly increased

Mathers and Levy (79), in order to appraise the prognostic value of the

anoxemia test, made a follow-up study in 1952, of 254 individuals on whom it was performed during the decade of 1937 to 1947. Included were 141 patients with manifest or suspected coronary heart disease, ten with hypertension and 103 with no evidence of a cardiovascular disorder. The average follow-up period was 6 years Sixty-three individuals died during the course of the study. In the 16 cases in which an autopsy was performed, the clinical diagnosis was confirmed. They felt that a positive reaction indicated not only the presence of coronary insufficiency at the time of the test, but also a poorer ultimate prognosis with respect to longevity. This conclusion was particularly applicable to the patients subject to anginal pain. Mathers and Levy point out, however, that whereas this is true for the group as a whole, it did not necessarily apply to the individual patient. In other words, because of numerous uncontrollable variables affecting the lesions of atherosclerosis, it is not possible to predict accurately, within a wide range of probability, the future clinical course of the patient with coronary heart disease by the use of the anoxemia test.

CRITIQUE OF STRESS TESTS

The criteria for the selection of a reliable stress test involve:

1. The efficacy of the test, that is, the number of true positives and true negatives.
2. The lack of severe complications, and
3. The per cent of false positive and false negative tests.

The exercise, anoxemia and ergonovine tests can each result in positive tests which fall into an 80 or more percentile bracket There is always a risk in performing these tests. Myocardial infarction or death may ensue Master (51) and Reeves and Harrison (55) have performed thousands of exercise tests without a fatal outcome However, this is not a universal experience (80-82) Wilson (80) states, "We had two patients die rather quickly after induced attacks of anginal pain and we are rather cautious in experimenting with these patients " Yu and Soffer (83) described a method of recording the electrocardiogram during the performance of a double two-step exercise test and were able to show that S-T depression, alteration of the T wave and appearance of ventricular premature beats actually occurred during exercise and persisted to the recovery period in most cases. This means that the patient usually continues to exercise during electrocardiographic alterations

Barker (23) holds "that the test which involves lowered oxygen tension does not appear to have a place in clinical medicine The ever present possibility of inducing convulsions and the relatively high incidence of sudden deaths makes it quite undesirable." Weinstein (84) feels that the ergonovine test has a greater margin of safety than the anoxemia or the exercise

test because the effect of the drug is rapidly produced and can be promptly nullified.

The ergonovine and anoxemia tests have the least reported incidence of false positive tests; the exercise tests the greatest False negative tests may depend on the amount of intimal sclerosis. Wegria (85) has shown that the presence of electrocardiographic changes in anesthetized dogs whose coronary flow is decreased experimentally, depends entirely on the per cent of such diminution. A reduction of blood flow of 10 to 35 per cent did not, as a rule, produce any electrocardiographic changes. With a reduction of 35 to 70 per cent, generally "slight" electrocardiographic changes in both the RS-T segment and T wave appeared Occasionally no change was seen and sometimes the RS-T segment and T wave changes were marked. With a reduction of 70 to 100 per cent, the changes were always marked. These changes were in the nature of elevation of the RS-T segment but this has been seen in angina pectoris (67-69)

In summary, that objective stress test which has the least percentile overlap between true and false positives would appear to be the most useful.

THE EXERCISE AND ANOXEMIA BALLISTOCARDIOGRAM

... exercise and anoxemia tests have been used with the ballistocardio- ... rdiogram (61, 40, 86). Davis *et al.* (61) found that ... cent of normal control subjects and in 31 4 per cent of patients ... mary artery disease deteriorated after exercise Scarborough *et al* (86) found control ballistocardiograms were all normal in form in the "normal" group and remained normal throughout the anoxemia test In 11 patients with suspected coronary artery disease, control ballistocardiograms were abnormal in 4, normal in 4, and borderline in 3 During anoxemia 1 normal, 2 borderline and 1 abnormal ballistocardiogram became abnormal or more abnormal

TOBACCO, THE BALLISTOCARDIOGRAM AND CORONARY ARTERY DISEASE

The normal ballistocardiogram has been shown to become abnormal after smoking for both the normal adult group (61, 40, 87-90) as well as those with coronary artery disease Such a conversion from a normal to an abnormal trace did not occur in the age group of 14 to 18 years despite the fact that the 100 high school youths tested were all habitual smokers (91). In the age group of 20 to 40 years, after testing 400 normal persons (250 ... 10 per cent of the ballistocardiograms became abnormal ... (92) found 28 per cent of 50 nor- ... smoking,

Davis *et al* (61) stud... ronary

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ment. Five year survival rates for patients with previous and subsequent myocardial infarction were about 46 per cent and 41 per cent, respectively. The 5-year survival rate for those with heart failure was about 20 per cent.

Electrocardiographic findings proved of some prognostic value. Those patients with angina pectoris and normal electrocardiograms lived longest, those with significant alteration of T and Q waves had a less favorable prognosis; and those with conduction disorder had the least favorable prognosis. The specific changes showed that the least favorable prognosis in 5-year survival studies were those with complete heart block, auricular fibrillation, and inversion of Wave T_1 and T_2. These conditions were also associated with the least favorable prognosis in 10-year survival studies, and, in addition, left bundle branch block was a grave prognostic finding in 10-year survival studies.

Angina pectoris associated with obesity or gall bladder disease had the most favorable prognosis; angina with diabetes mellitus or carcinoma, the least favorable. Thyroid disease and duodenal ulcer had an in-between effect on survival rate

Sigler's observations were made on 1,700 cases over a 25-year period (98). The average length of survival of the 679 patients who died was about 4.6 years. In the entire group the percentage of patients still living at the end of 5 years was 32 8 for males and 34 5 for females About 10 per cent of patients of each sex survived for 10 years Of the 1,021 patients still living, the average length of survival was about 5 5 years The percentage of patients living at the end of 5 years was 54 6 for males and 46.1 for females, at the end of 10 years about 15 per cent of each sex was still living.

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artery disease. The normal persons ranged in age from 25 to 74 years with an average of 47.7 years; the patients from 29 to 68 years with an average of 49.0 years Ballistocardiographic alterations after smoking occurred in 6 8 per cent of the normal control subjects and 58.6 per cent of patients with coronary artery disease. Pordy (90) found alterations post-smoking in 53 per cent of a cardiac group.

The causes of the changes in the ballistocardiogram after smoking are not known but the high incidence of post-smoking alterations in the ballistocardiogram of the patient with coronary artery disease has led to the suggestion that the tobacco sensitive group give up smoking This is not unlike the problem of tobacco angina in which chest pain and depression of the S-T segment of the electrocardiogram in depth to that after the stress tests may occur after smoking in the tobacco sensitive person (88, 61, 93-95, 95a, 96)

BLOOD TESTS IN THE DIAGNOSIS OF CORONARY INSUFFICIENCY

Serum cholesterol, serum lipoproteins, the atherogenic index and the phospholipid cholesterol ratio in relation to arteriosclerosis have been considered in Chapter I In my opinion (33), these tests lack specificity as diagnostic aids in coronary insufficiency in the individual patient because of the overlap of normal and abnormal, within the normal range of the tests.

PROGNOSIS OF ANGINA PECTORIS

The largest series of follow-ups are those of Block, Crumpacker, Dry and Gage (97) who made observations in 6,882 cases and Sigler (98) who followed 1,700 cases.

The Block group represents an average follow-up period of 18 years with a range of 5 to 23 years. The average age at diagnosis of angina pectoris was 58 8 years for the total series, 58 5 years for the males and 60 1 years for the females. The average duration of symptoms prior to diagnosis was 2.5 years. The ratio of males to females was about 4 to 1

Survival studies showed that mortality was greatest in the first year (about 15 per cent) and about 9 per cent per year thereafter. The survival curve for the entire series is lower than the normal population Females had a better prognosis than males The 5-year survival rate for the entire population was 58 4 per cent as compared to the rate of 86 9 per cent for the normal population The 10-year survival rate for the entire series was 37 1 per cent as compared to the normal rate of 70 4 per cent.

Factors which unfavorably influenced the prognosis included cardiac enlargement, hypertension, myocardial infarction and congestive heart failure. At the end of 5 years, about 64 per cent of patients without cardiac enlargement were living as contrasted to about 41 per cent with cardiac enlarge-

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Chapter III

Differential Diagnosis of Chest Pain

AS STATED by Reeves and Harrison (1). "When a patient complains of pain in the chest two separate questions often need be answered The first involves a decision as to whether or not pain results from disturbances of the coronary circulation The second question, which arises only when the first is answered in the negative, involves a positive decision as to the cause of the pain. When a patient is told that his pain is not the result of coronary disease, he naturally wonders what may actually be the cause. Unless this problem can be solved in a manner convincing to the patient, he may continue to believe that the heart is responsible. Such a belief is likely to lead to months or years of unnecessary fright and anxiety on the part of the patient and his relatives"

Pain arising from thoracic structures other than the coronary arteries may simulate that of angina pectoris or myocardial infarction to a remarkable degree On the other hand, there are certain diseases in which angina pectoris of coronary sclerotic origin may occur concomitantly. These include hyperthyroidism (2, 3), hypothyroidism (4, 5), diabetes mellitus (6), hypertension (7), peptic ulcer (8) and cholecystitis (9)

By 1938, Herrick (10), who had delineated so clearly the clinical picture of coronary thrombosis 26 years before, had compiled a list of 30 clinical conditions which had been mistaken for acute coronary thrombosis. Some of the more important clinical conditions from which pain of coronary artery origin must be differentiated are listed below.

1. LESIONS OF THE VASCULAR SYSTEM

a. **Aortic Disease:** Uncomplicated syphilitic aortitis may be accompanied by substernal pain. This pain is localized and is not influenced by exertion (11) This is to be contrasted with the pain of coronary ostial stenosis which resembles the typical pain syndrome of angina pectoris (12-14) This is not surprising since the diminution of blood supply through the narrowed mouths of the coronary arteries leads to myocardial ischemia as in coronary artery disease due to arteriosclerosis. The diagnosis of coronary ostial stenosis depends upon the history of syphilis or a positive serology in the absence of signs of arteriosclerosis.

b. **Aortic Valvular Dis**[illegible] tic stenosis and angina pectoris [illegible] er cent (16), 36 7 per cent (17), [illegible]

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likely to have chest pain as those without aortic insufficiency (31). The usual explanation of the pain of aortic insufficiency is that the lowered diastolic pressure decreases the amount of coronary flow since the greater proportion of coronary filling takes place during diastole.

c. Mitral Stenosis: Angina pectoris or coronary thrombosis is a rare occurrence in mitral stenosis (32, 33). Levine and Kauvar (32) found an incidence of only 0 6 per cent of mitral stenosis in 2,832 cases of angina pectoris or myocardial infarction. The occurrence of pain in mitral stenosis has been attributed to a relative coronary insufficiency (33); compression of the left coronary artery in its course between the left auricle and a prominent pulmonary conus (34), and to a pull on the coronary orifice as a consequence of a contraction of a scarred mitral valve and the shortened chordae (35).

Three other types of chest pain have been found associated with mitral stenosis (36), namely, that of cardiac neurosis, that of active rheumatic carditis and that of hypercyanotic angina. This last syndrome is described as one of severe pain in the precordium or retrosternally with radiation to the left shoulder and arm but without any relation to exertion, emotion or stress The attacks are paroxysmal in nature and can last for hours or days. Signs of dyspnea, orthopnea, and a severe degree of cyanosis (from which sign the syndrome gets its name) are prominent. During the attacks, signs of pulmonary congestion are few. There is usually no fever or leucocytosis The pain is more effectively relieved by oxygen than by vasodilator drugs.

d. Dissecting Aortic Aneurysms: The coronary arteries, as they rise from the aortic sinuses, may be compromised by disease of the ascending aorta. Medical dissection of the aorta in this region with an extension of the dissection in the intrapericardial portion of the aorta may cause obliteration of the coronary circulation and produce myocardial infarction (37, 38) Reports have appeared in which dissecting aneurysms have involved the right coronary artery (39, 40), the left coronary artery (41), and even the mouth of both coronary arteries (42). The helpful points in this diagnosis are sudden onset of chest pain in a patient with hypertension who develops an aortic insufficiency where one has not been present previously (43). The electrocardiogram may simulate that of myocardial infarction closely or may show changes of acute local myocardial ischemia, that is, T wave inversion rather than deep Q patterns such as seen in acute anterior or posterior wall infarction The latter is believed due to the fact that the dissecting column of blood with the hematoma thus formed compresses rather than obliterates the entire vessel and leads to partial rather than total ischemia Logue and Sikes (44) describe pulsation of the sternoclavicular joint as a sign of diagnostic significance

When the dissection of the thoracic aorta is distal to the pericardial

Kumpe and Bean (18) believe that the typical symptom complex of transitory substernal pain provoked by exercise, emotion, or exposure to cold is rare in association with aortic stenosis. There is, however, general agreement (15, 16, 18-20), that the degree of coronary sclerosis tends to run inversely proportional to the degree of aortic stenosis.

Contratto and Levine (15) examined the coronary arteries at necropsy of 2 males, aged 46 and 25, who had clinical and pathological evidence of aortic stenosis and clinically complained of angina pectoris. They found perfectly normal coronary arteries and no recent or old infarctions of the ventricle They attributed the pain to a suction-like effect on the smaller coronary orifices by the increased velocity of the blood flow through the aorta This resulted in a decreased flow through the coronary arteries and a relative myocardial ischemia

This factor of coronary insufficiency in producing the anginal pain in aortic stenosis is strengthened by the findings of Friedberg (21) of acute myocardial damage at necropsy in hearts with aortic stenosis and normal coronary vessels Occasionally, the clinical picture of acute coronary thrombosis may be simulated by calcific aortic stenosis without any pathologic evidence of myocardial infarction (22) Calcification of the aortic valve and even of the coronary arteries may co-exist without any symptoms of coronary insufficiency (23). It is to be remembered calcification of the ascending portion of the aortic arch is a sign of luetic and not arteriosclerotic involvement (24)

If one, therefore, is to make a diagnosis of angina pectoris on the basis of coronary artery disease in the presence of aortic stenosis, such more usual clinical concomitants as old age, the presence of diabetes and/or hypertension, and electrocardiographic changes, should bear more weight than the presence of aortic stenosis itself.

Cardiac pain in free aortic insufficiency, such as in syphilitic heart disease, is usually due to an associated narrowing of the coronary orifices Without this association angina pectoris is rare.

However, a specific type of anginal pain syndrome has been described in aortic insufficiency of rheumatic origin (25-30) The chest pain is similar to that of angina pectoris of coronary artery origin in its location, radiation and onset with effort. It differs mainly in the occurrence of the seizures at night while at rest Relief is obtained by nitroglycerin or in some instances by getting up and walking about There are prominent vasomotor features such as flushing, sweating, palpitation and throbbing of the neck vessels. Lewis (27) felt that the pain was brought on by a relative coronary insufficiency due to a rise in blood pressure and pulse rate which preceded the pain

Patients with coronary sclerosis and aortic insufficiency are twice as

the T-waves compatible with a diagnosis of coronary insufficiency. Even relief by nitrites does not necessarily signify that one is dealing with coronary artery pain, because a placebo sometimes appears to be equally effective in effort angina and because nitrites have been found occasionally to relieve skeletal muscle pain.

What diagnostic criteria distinguish somatic from cardiac pain syndromes of the chest? In acute episodes of pain suggestive of myocardial infarction, the presence or absence of signs of tissue necrosis and circulatory collapse is of the utmost importance in weighting the diagnosis in one direction or the other. The absence of trigger areas would seemingly rule out the skeletal muscles as a cause of pain, unless, of course, the trigger areas happened to be located in the retro-sternal striated muscles of the chest wall which would not be accessible to palpation. That the pain syndrome is primarily somatic in origin is often suggested by a "rheumatic tendency" of the patient, or the finding of painful motion elsewhere in the body attributable to trigger areas in appropriate muscles. In chronic effort syndromes, the most valuable sign of a somatic disorder is an enormous variability in the exercise limit, or capacity for effort without pain, over short periods of time. In our experience, such variability is uncommon in coronary artery disease; in true effort angina, just as in intermittent claudication, pain appears after walking approximately the same distance, within narrow limits, from day to day. On the other hand, if the distance which the patient can walk fluctuates widely, it is likely that there is an extracardiac component in the etiology of pain.

Solomon and Winter (50) have reported a case of chest pain due to an intramuscular lipoma.

3. LESIONS OF THE NERVOUS SYSTEM

a. Herpes Zoster: The chest pain in herpes zoster may precede the vesicular eruption by a few days and, if it involves the left side of the chest, it may be mistaken for a more serious heart condition until the rash appears (10, 51).

b. Brachial Plexus: Affections of the brachial-plexus must be divided into those involving the trunks or the cords. Involvement of the trunks of the brachial plexus causes radicular symptoms and is brought on by lesions near the scaleni muscles or vertebral column and high in the supraclavicular fossa and axilla It is with lesions of the trunks that we results in peripheral nerve lesions and is brought on by lesions low in the supraclavicular fossa and axilla. It is with lesions of the trunks that we are more concerned

c. Nerve Lesions Secondary to Osteoarthritis of the Spine: The intervertebral foramina, through which spinal nerve roots emerge, are com-

reflection, the symptoms usually produced are cough, hemoptysis and a persistent tearing pain in the chest. This may be accompanied by shock with a decided fall in blood pressure from previous hypertensive levels. Roentgenograms may show widening of the thoracic portion of the aorta. Angiocardiographically (45), the aortic lumen is seen to be more or less abruptly narrowed and the aortic walls thickened at the site of dissection Contrast substance may be seen within the false passageways as a result of the dissection

2. LESIONS OF THE MUSCULAR SYSTEM

Reports from different parts of the world have called attention to somatic pain syndrome of the chest and our experience (46-48) indicates that these disorders have not always entered into the consideration of the physician as a cause of chest pain. The skeletal muscles which are usually involved in these pain syndromes include such anterior chest muscles as the pectoralis major (48) and minor (49), the sternalis and the serratus anterior, such posterior chest muscles as the infraspinatus, supraspinatus and posterior superior serratus When shoulder and arm pain becomes a problem in differential diagnosis from angina pectoris or coronary thrombosis, the scalenus anticus syndrome must be considered.

These pain syndromes of the chest muscles which are primarily somatic in origin may at times resemble effort angina and myocardial infarction. Myofascial trigger mechanisms may be initiated by direct trauma to muscle or joint, chronic muscular strain, chilling of fatigued muscle, acute myositis, arthritis, nerve root injury, visceral ischemia or dyskenesia, and hysteria. Predisposing factors may be general fatigue, low metabolic rate with creatinuria, chronic infection and psychogenic stress. Protracted myofascial pain following activation of trigger area is thought to depend on a reflex pain cycle maintained by the trigger area.

Our observations are in conflict with the frequently encountered view that when pain on effort (walking) is *substernal*, it is necessarily due to coronary artery disease, whereas when it *is located in the precordium*, it may originate from either cardiac or somatic causes. We have found, also, that certain other criteria which are often accepted as pointing toward a cardiac etiology of chest pain can no longer be regarded as reliable The intensity and quality, as well as the distribution, of so-called cardiac pain, can be reproduced in every detail by the referred pain momentarily induced by stimulation of trigger areas in the chest muscles Furthermore, we can no longer depend with certainty on transient electrocardiographic changes if the electrocardiogram was taken during an attack of pain, as it often is, since extracardiac pain induced, for example, by work-ischemia of the forearm muscles, may temporarily produce abnormalities of

while head movements did, and that a normal physical examination and electrocardiogram were found excepting for a sensitive right carotid sinus.

4. LESIONS OF THE BONES

a. Tietze's Syndrome: This syndrome is described as a painful, benign, nonsuppurative swelling of the costochondral or the sternoclavicular junction (58-61). Tender bullous or fusiform swelling involves the soft tissue, cartilage and bone. There are no diagnostic radiographic alterations.

b. Cervical Rib: The first rib is the base of a triangle in the neck of which the scalenus anticus muscle anteriorly and the scalenus medius posteriorly form the other two sides The subclavian artery and the brachial plexus pass within the borders of this triangle When this area is compromised so that pressure on the nerves or the vessel results, a series of symptoms gnown as the scalenus anticus syndrome results The presence of an anomaly, such as a cervical rib, or spasm of the scalenus anterior muscle may be the causative factors Pressure on the brachial plexus may cause pain simulating either angina pectoris or coronary thrombosis (61).

The scalenus anticus syndrome is further characterized by pain in the chest, neck, arms or hands, signs of venous obstruction, vasomotor changes, and, if severe, by evidences of arterial insufficiency and damage to the motor and sensory nerves

The presence of a cervical rib is easily determined by x-ray. The presence of the scalenus anticus syndrome is suggested (63) by fullness in the supraclavicular space, poor grip, diminished or absent reflexes, and by the intensified pain produced by compression of the anterior scalenus muscle on the affected side as compared with the normal side. Allen has developed the following maneuver to aid in the diagnosis (64): "The patient sits with arms extended horizontally at the shoulders and flexed at the elbows so that the forearm is perpendicular The head is then rotated as far as possible either toward or away from the side being tested. A positive result is indicated by marked diminution of, or complete disappearance of, pulsations in the radial artery as determined by the physician's fingers."

The tender spots in the anterior scaleni muscles which may be elicited by digital pressure respond to procaine infilteration and the resultant release of spasm may be both diagnostic and therapeutic.

Judovich (63) feels that scalenus syndrome may also follow myocardial infarction He feels that this results through reference of pain in the sensory distribution of C_3, C_4 and C_5 segments. With adequate stimulation, the spasm of the anterior scalenus muscle develops as a sensory-motor complex.

c. The Hypersensitive Xiphoid: Lipkin, Fulton and Wolfson (118)

pletely surrounded by bony structures, and osteophytes produced by cervical arthritis may irritate the nerve root and produce radicular symptoms (52).

Davis (53) has shown how closely the syndrome of radiculitis with chest pain may simulate angina pectoris or coronary occlusion. Besides the usual symptoms of coronary disease, certain characteristics of radiculitis are also present, such as attacks occurring while at rest in bed at night, or after certain movements of the spine, to wit, bending, turning from side to side or getting out of bed, and finally, after coughing, sneezing or straining at stool. In Davis' series of patients, hypertrophic osteoarthritis was present in those patients in whom roentgenograms of the cervicodorsal spine were taken. The more important diagnostic point was the reproduction of attacks by the application of pressure over the dorsal vertebrae. Occasionally, tenderness in the region of the costochondral junctions of the ribs and sternum was present. Diagnosis was confirmed in some by the striking response to therapy which consisted of postural correction, bed boards, exercise and, particularly, manipulation and traction of the cervicodorsal spine

d. Nerve Lesions Due to Rupture of the Sixth Cervical Intervertebral Disk: It has been pointed out (54-56) that precordial pain may be due to unilateral pressure on the sixth cervical nerve root In the four patients of Semmes and Murphy (54) each gave a history of numerous cricks in the neck recurring intermittently months or even years before the initial attack of radiation pain In each patient, the pain radiated to the precordium as well as to a point just medial to the upper angle of the scapula and down the lateral and medial surfaces of the arm On physical examination, they found severe muscle spasm in the neck and shoulder with an exquisitely tender point just posterior to the scalenus anticus muscle over the exit of the seventh cervical nerve from the spinal canal X-ray examination of the cervical spine showed a straightening of the cervical curve. No hypertrophic arthritis was found at the beginning of symptoms The treatment consisted in removal of the herniated disk.

e. Hyperactive Carotid Sinus: Friedman (57) reports 2 cases of young men (aged 35 years and 21 years) in whom the clinical manifestations of a hyperactive carotid sinus simulated angina pectoris. One of these patients complained of pain in the substernal area with radiation to the left shoulder. Both patients were adamant in their insistence that exercise or exertion did not produce chest pain but that sudden movement in the neck did. However, one of the patients, who was a physician, admitted relief of the chest pain by amyl nitrite after the occurrence of one of the attacks while lifting a heavy object. The differential diagnosis was made by the facts that vertigo frequently preceded the chest pain, that strenuous exertion or heavy work did not always induce the chest pain

with the pain, (3) presence of pain on breathing, (4) the clinical evidence of right ventricular hypertrophy, and (5) the minimal or lack of response to nitroglycerin.

6. LESIONS OF THE GASTROINTESTINAL TRACT

a. Cardiospasm: Cardiospasm with or without megaesophagus will give substernal pressure or pain which may closely simulate angina. The occurrence of pain after meals, regurgitation of food and x-ray confirmation of spasm with a dilated esophagus is useful in the differential diagnosis.

b. Peptic Ulcer of the Esophagus: The clinical features of this disease are pain, hematemesis and dysphagia (67). The pain is located at the lower end and behind the sternum. It is made worse on lying down. This pain radiates on occasion to the back, both shoulders and sometimes down one or both arms. Esophagoscopy is of aid in revealing the ulcer. Peptic ulcer of the esophagus is nearly always associated with a congenitally short esophagus and a diaphragmatic hernia, both of which can be revealed by roentgenograms taken after swallowing barium

c. Esophageal Hiatus Hernia: A hiatus hernia may give symptoms indistinguishable from those of angina pectoris (68-71, 119) or a myocardial infarction (72, 73). In a series of 91 small hiatus herniae (maximum diameter not over 7 cm) and 37 cases of large herniae (74), substernal pain was found in one-third of the former and approximately one-seventh of the latter patients Small hiatus herniae therefore are more important in the differential diagnosis from angina pectoris The more common symptoms in hiatus hernia are epigastric pain and vomiting or regurgitation Right shoulder pain in hiatus hernia is more common in the absence than in the presence of heart disease. Consistently recurring substernal pain on effort is rare in hiatus hernia. The act of bending forward or lying down usually brings on the symptoms of hiatus hernia Although the use of nitroglycerin in hiatus hernia may cause dramatic relief on occasion, it does not have the consistency of relief which is found in its use in angina pectoris. On the other hand, atropine is more effective in relieving the pain of hiatus hernia

Maisel and Horger (120) report on the use of pneumoperitoneum to distinguish between the chest pain of hiatus hernia and coronary artery disease A 60-year-old man under their care had precordial pain and on work-up was found to have a positive Master's exercise tolerance test and a hiatus hernia The patient's pain had practically invalided him before a trial with pneumoperitoneum successfully relieved it. On this basis, because the authors felt that the pain rose chiefly as a consequence of the hiatus hernia, a hernioplasty was done. The patient returned to work pain-free and an exercise tolerance test done eight months after the operation was still positive A conclusion is reached that pneumoperitoneum affords a diagnostic

have reported a frequent association between coronary artery disease and a tender xiphoid. The diagnosis is made by palpation of the xiphoid area This reproduces the spontaneous pain of which the patient has complained Very moderate finger tip pressure will elicit the syndrome. The methods of treatment include local procaine infiltration, ethyl chloride spray and xiphoidectomy Because the pain is most commonly experienced deep in the chest somewhere behind the sternum and may radiate into the epigastrium, through to the back, to both shoulders, to the arms or over the precordium, reassurance must be given the patient that this pain is not cardiac in origin

5. LESIONS OF THE RESPIRATORY SYSTEM

a. Acute Pleuritis: Chest pain secondary to inflammation of the pleura is aggravated by deep inspiration and accompanied by a diagnostic friction rub elicited by auscultation.

b. Pulmonary Embolism: The chest pain associated with a relatively large pulmonary embolism may be sudden in onset and substernal in location (65) Just as with acute myocardial infarction, dyspnea, cyanosis, sweating, weakness, fall in blood pressure, weak pulse, vomiting and a rise in temperature may be present after a pulmonary embolus Such signs as moist rales in the lungs, hemoptysis, and elevation of one leaf of the diaphragm are signs related to the embolus itself The electrocardiogram may be diagnostic of acute cor pulmonale, that is, a deep S_1, significant Q_3 and inverted T_3 pattern A history of an acute or recent thrombophlebitis or the onset of these symptoms one to three weeks after an operation, a delivery or an injury may point toward the probability of an embolism.

c. Spontaneous Pneumothorax: This disease is due to the rupture of a vesicle on the surface of the lung. The chest pain is sudden in onset due to pleural rupture and may be accompanied by shortness of breath Respiratory movements on the affected side are diminished. The percussion note is hyperresonant The breath sounds are suppressed and roentgenograms show evidence of a pneumothorax.

d. Pulmonary hypertensive pain: Viar and Harrison (66) described a group of patients suffering from chest pain related to an increased pressure in the pulmonary vascular circuit. The diagnoses included: (1) lesions of the mitral valve, (2) certain congenital anomalies of the heart; (3) primary diffuse disorders of the lungs, especially asthma and emphysema, or (4) disorders of the pulmonary artery and, more particularly, embolism The chest pain may be similar to that produced by coronary artery disease insofar as location, radiation, quality and intensity of the pain are concerned. The differential is to be made by (1) the recognition of an underlying condition capable of causing pulmonary hypertension, (2) cyanosis occurring along

with the pain, (3) presence of pain on breathing, (4) the clinical evidence of right ventricular hypertrophy, and (5) the minimal or lack of response to nitroglycerin.

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test for distinguishing, in patients with co-existing angina and hiatus hernia, those cases of chest pain that are of cardiac origin from those that are not.

d. Association of Gall Bladder Disease and Coronary Artery Sclerosis: There are three points of importance in the relation of gall bladder disease and coronary artery disease. (1) that there is a positive statistical association between gall bladder disease and coronary artery disease (9, 75) and this association becomes more definite after the age of 40 (77); (2) that a striking improvement in the symptoms of angina pectoris may follow the removal of a diseased gall bladder in patients with coronary artery disease, and (3) that gall bladder disease alone may give rise to symptoms simulating angina pectoris in patients with no evidence of coronary sclerosis (78, 79)

The importance of chronic cholecystitis as a factor in myocardial incompetence was first indicated by Babcock (80) in 1909. Studies on the association of gall bladder disease and coronary artery disease in autopsied cases (9, 77) are sufficiently convincing to regard this relation as important. Furthermore, Fitz-Hugh and Wolferth (81) were able to demonstrate the relief of symptoms suggestive of coronary insufficiency and the return of inverted T waves in the electrocardiogram to an upright position following the removal of gallstones The experimental proof for this possibility is offered by Gilbert (82) who demonstrated a decrease in coronary blood flow on distension of the gall bladder or distention or irritation of its ducts. Ravdin (83) reports the history of a 48-year-old white female who, 6 months after a cholecystectomy, began to have precordial pain which radiated through to the back and down the ulnar aspect of the left arm to the fingertips. This pain was sometimes relieved by nitroglycerine *A celiotomy* revealed a thick, kinked common duct plastered with adhesions and containing sand, but no stones The duct was freed of adhesions and a T-tube left in place Post-operatively, all traces of precordial pain disappeared This pain could be reestablished by distention of the common duct through the T-tube. It was felt that reflexes arising in the extra-hepatic bile passages caused a restriction in the coronary flow sufficient to produce the symptoms of angina pectoris. This is in line with the findings of Gold (84) who studied the effects on the electrocardiogram of extracardiac pain produced by a blood-pressure cuff applied to the arm or by a head-vise Changes in the T waves were found at the height of the pain.

Wakefield (85) sums his experience by stating, "It is my conviction that in coronary artery disease and its most common clinical manifestation, either angina pectoris or myocardial infarction, associated with chronic gall bladder disease, with or without stones, cholecystectomy should be *seriously* considered, provided the patient's cardiac status warrants the surgical procedure."

Ravdin and his group (117) state that operation upon the biliary tract should not be undertaken for the purpose alone of relieving anginal pain unless there is a relationship between the biliary tract and the anginal seizures. Also, the presence of angina pectoris should not be regarded as a contra-indication to an operation upon a diseased biliary tract unless the cardiac involvement is so advanced that the operative hazard outweighs the chance of benefit. In some patients true angina pectoris can be ameliorated or completely relieved by gall bladder surgery. It is important to note that in the period of 1944 to 1947, inclusive, 106 patients with cardiac disease were operated upon for gall stone disease with no deaths.

Keys, Dry, Walters, and Gage (121) reviewed the records of 100 patients with coronary artery disease who had undergone cholecystectomy in the 5 years between 1948 through 1952 in order to answer two questions: How well do patients with coronary heart disease tolerate cholecystectomy? Does the removal of a diseased gall bladder influence the subsequent clinical course of the patient with coronary heart disease? Eighty of the patients had angina pectoris, 31 had a history consistent with a previous myocardial infarction There were no deaths on the operating table Three patients died in the hospital, only 1 of these was due to vascular complications One patient had an acute myocardial infarction post-operatively from which he recovered Two other patients had clinical and electrocardiographic evidence of acute coronary insufficiency while in the hospital.

The survival rate of these patients 6 years after operation was 70 6 per cent as compared with 83 9 per cent in the normal population of similar sex and age Keys, Dry, Walters and Gage (121) conclude "it is doubtful whether removal of a diseased gall bladder influences the course of coronary artery disease directly but it is likely that life may be prolonged by performance of cholecystectomy preferably during the quiescent phases of gall bladder disease."

e. Acute Pancreatitis: Acute pancreatitis may be associated with an acute onset of substernal oppression as well as epigastric pain and may be confused with an acute myocardial infarction (86) This differential diagnosis may be rendered more difficult when arrhythmias such as auricular fibrillation or flutter are associated with an onset of acute pancreatitis (87), or when electrocardiographic abnormalities suggestive of myocardial infarction accompany the acute pain (88) Gottesman, Casten and Beller report on 5 proven cases of acute pancreatitis in whom there were found electrocardiographic changes suggestive of myocardial infarction Further they were able to reproduce these electrocardiographic changes in dogs with experimentally induced acute pancreatitis. The differential diagnosis is made by the presence of an elevated blood amylase and signs of upper abdominal peritoneal irritation which is found in acute pancreatitis.

f. **Splenic Flexure Syndrome:** Machella (89) described a group of 40 patients in whom a symptom complex consisting of pain or discomfort in one or more of the following sites. The left upper quadrant of the abdomen, the precordial area, chest, left shoulder, neck or arm was caused by distention of the splenic flexure. Symptoms occurred when gas was visualized in that area. Gas was absent during asymptomatic intervals and symptoms could be reproduced by distention of the splenic flexure by air inflation of a balloon introduced through the rectum.

7. LESIONS OF THE MEDIASTINUM

Acute mediastinitis which follows rupture of the esophagus is usually traumatic in origin However, spontaneous perforations may follow severe vomiting (90, 91). In the course of this vomiting, there is severe precordial or epigastric pain, or both, with associated shock and dyspnea The later finding of pleural effusion or subcutaneous emphysema is helpful in the differential diagnosis

Pulmonary alveoli of healthy persons may rupture and allow air to escape into the surrounding connective tissue without any evidence of trauma to the chest Interstitial mediastinal emphysema may result. The patient that attracted Hamman's attention (92) to the diagnosis of sponaneous mediastinal emphysema was a 51-year-old male who while shaving was suddenly seized with intense pain under the sternum which radiated to the left shoulder. This pain lasted one-half hour. Physical examination and the electrocardiogram were normal. Three days after the onset, the patient reported that while lying on his left side, he had heard a curious loud bubbling, cracking sound synchronous with the heart beat This was misinterpreted as a pericardial friction rub and was used to further confirm the probably diagnosis of coronary thrombosis. This clinical picture remained a mystery until 4 months later when Hamman heard the same characteristic crunching, bubbling sound in a 17-year-old boy who had a sudden onset of substernal pain while sitting. There was subcutaneous crepitation over the front of his neck and a roentgenogram showed air in the mediastinal tissue between the heart and the anterior wall of the chest

Aisner and Franco (93) list four signs as being of importance in the diagnosis of mediastinal emphysema (1) mediastinal crepitation, (2) decrease or obliteration of cardiac dullness, (3) subcutaneous emphysema, and (4) pneumothorax. They point out that pneumothorax is most often left sided This adds to the complexities of the differential diagnosis from pain in the chest of cardiac origin

Tumors of the mediastinum, both benign and malignant, manifest symptoms by pressure or irritation of the mediastinal structures. Their presence is confirmed by x-ray examination of the chest Fishberg (94) describes a

patient with a mediastinal neoplasm who had status anginosus for 16 hours before death. At necropsy, the tumor mass surrounded and obliterated the left circumflex artery and it was postulated that this might be the cause of the precordial pain.

8. LESIONS OF THE PERICARDIUM

Acute pericarditis has precordial pain as one of its characteristic symptoms (95-100). Just as in coornary occlusion this pain originating over the precordium may radiate to the left shoulder, left side of the neck, and to the left arm This pain is associated with dyspnea when effusion accompanied the acute pericarditis (101). Acute pericarditis may arise in the course of other diseases, such as acute rheumatic fever, tuberculosis, uremia, Libman-Sacks, lues or parasitic disease. There is an acute benign pericarditis of unknown etiology which has been chiefly noted in young patients after an infection of the upper respiratory tract Acute pericarditis may also occur secondarily to myocardial infarction. The differential of all the foregoing from pericarditis associated with coronary artery disease should be made first on the presence of some primary disease which could produce pericarditis The presence of a friction rub is of no differential help The electrocardiographic picture differs in acute pericarditis as compared with that of myocardial infarction The characteristic electrocardiogram in acute pericarditis involves an RS-T elevation in all leads with later inversion of T waves. Q waves are rarely present and rarely significant in acute pericarditis In acute myocardial infarction, one sees a reciprocal relation in the RS-T segment between leads I and III Q waves when present are deep and significant

When effusion accompanies pericarditis there may be compression symptoms such as hacking cough, hoarseness or dysphagia There will then be signs of increase in cardiac dullness, diminished heart sounds, Ewart's sign, diminution in the pulse pressure, and a paradoxical pulse X-ray will reveal a water-bottle type of heart, which on fluoroscopy will show diminished or absent pulsations of the borders

9. HEMATOLOGIC DISEASES

Herrick was one of the first to call attention to the association of angina pectoris and anemia (102) In pernicious anemia (103) such cardiac symptoms as dyspnea, palpitation, tachycardia and precordial pain may be present. The physical findings may include edema of the ankles, apical systolic murmur, an enlargement of the heart and liver. Pickering and Wayne (104) treated 8 anemic patients who complained of pain over the sternum induced by exercise (step-test) and relieved by rest The causes of anemia included hemorrhage from hemorrhoids, chronic microcytic anemia, pernicious ane-

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than the usual paroxysm of true angina pectoris. The dull type of FCVD precordial pain is so characteristic that it need never be confused with true angina pectoris"

It is to be remembered (115, 116) that anxiety states may occur in patients with coronary artery disease and emotional disturbances may bring on anginal attacks. An attack of angina pectoris can readily become associated in the mind of the patient with other anxiety-provoking experiences and situations. In this way, angina pectoris may become the current focus and point of discharge for earlier significant anxieties (115). These anxieties may lead to a "cardiac neurosis" in a patient with true angina The pain of angina is lightly dismissed by some patients. In others, it may result in angor animi with a sense of imminent dissolution, an overwhelming fear of impending death.

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mia and recurrent hematemesis. After cure of the anemia, 6 patients were completely relieved of the sternal pain on exercise. This would indicate as pointed out by Willius and Giffin (105) that the anginal syndrome was due to anoxia of the myocardium, secondary to the anemia rather than to coronary sclerosis.

A clinical picture simulating coronary occlusion has been reported (106) during a hemolytic crisis in sickle-cell anemia

10. LESIONS OF THE DIAPHRAGM

Boas and Boas (107) report the history of a patient who was seized with severe pain in the precordium and left side of the chest. A diagnosis of coronary thrombosis had been tentatively made but he actually had trichinosis with diaphragmatic involvement Other acute inflammatory conditions of the diaphragm have been described under the title of Hedblom's Syndrome (108)

A case of diaphragmatic flutter of from 70 to 300 minor contractions a minute has been reported as causing precordial pain with radiation to the left shoulder and down the left arm (109, 110)

11. FUNCTIONAL CARDIOVASCULAR DISORDER*

Precordial pain is one of the prime symptoms of this disease Two types of precordial pain have been described (111, 112). One is a poorly localized, dull ache which is seemingly more uncomfortable than painful and which fits in with the type of pain discussed under lesions of the muscular system Wood (113) has maintained that the intercostal muscles may develop painful spasm because these patients tend to breathe more with the chest wall than with the diaphragm This is also associated with overbreathing (114).

Friedman (111) has also described a sharp, transient, stabbing type of pain located at the left nipple and radiating inside the chest. He found that the onset of this pain was in some instances with an arrhythmia and believed that it represented a true pain of cardiac origin

The differential diagnosis between angina pectoris and precordial pain of functional cardiovascular diseases is listed by Friedman (111). "Certain differential points however are dependable Thus, precordial pain of FCVD origin rarely extends to the sternum, shoulders or arms It also is not uniformly provoked by exercise and *never is* unless there is excessive tachypnea. The sharp type of FCVD pain usually occurs in association, as has been mentioned, with some abnormality of cardiac function (usually arrhythmia). Moreover, this last type of pain rarely if ever occurs during sleep, is uninfluenced by meals or by climatic changes It also is shorter in duration

* This syndrome has also been called "irritable heart," "soldiers' heart," "effort syndrome," and "neurocirculatory asthenia"

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As for smoking, I have already alluded to the deleterious effects of cigarets on the ballistocardiogram in patients with coronary artery disease and to the sensitivity of patients to tobacco resulting in precordial pain and on occasion, electrocardiographic alterations (Chapter II) Levy (3, 4) found no great difference in the effects of nicotine on the circulation of normal subjects and in cardiac patients, except in susceptible individuals. Von Ahn (5) has indicated that the effect of nicotine on the coronary circulation even with hypoxia is due to the sympathetic effect with an increase in heart rate which in turn causes T-wave inversion and S-T depression Both of these electrocardiographic effects are eliminated by

TABLE 9
1200 CALORIE DIET

Food	Weight	Measure	C	P	F
Breakfast					
Fruit	100 gm	1 serving	15		
Egg	50 gm	1 medium		7	5
Bread or equivalent	30 gm	1 slice	15	3	
Skimmed milk	200 gm	6 oz	10	6	
Coffee					
Dinner					
Soup, clear					
Meat or equivalent*	90 gm	3 oz		21	15
Vegetable*	100 gm	½ cup	7	2	
Salad					
Bread or equivalent	60 gm	2 slices	30	6	
Fruit	100 gm	1 serving	15		
Tea					
Supper					
Meat or equivalent*	60 gm	2 oz		14	10
Vegetable*	100 gm	½ cup	7	2	
Salad					
Bread or equivalent	30 gm	1 slice	15	3	
Fruit	100 gm	1 serving	15		
Skimmed milk	200 gm	6 oz	10	6	
Coffee					
Night Feeding					
Skimmed milk	200 gm	6 oz	10	6	
Soda crackers	12 gm	2	10	2	
Totals			159	78	30

*Approximate Composition***

	Unit	Amount		Unit	Amount
Calories		1210	Vitamin A	I U	19,750
Carbohydrate	gm	160	Thiamine	mg	1
Protein	gm	75	Riboflavin	mg	1 8
Fat	gm	30	Niacin	mg	12
Calcium	gm	1	Ascorbic Acid	mg	125
Iron	mg	12			

* Cooked
** This diet is adequate according to the Recommended Daily Dietary Allowances of 1948 (From Diet Manual, Beth Israel Hospital, New York, N Y)

CHAPTER IV

Treatment of the Patient With Effort Angina

THE PATIENT with effort angina is most always an ambulatory patient and treatment is directed at preventing anginal attacks during measured work, ambulation and exercise or to terminate the attack immediately when it occurs. Toward this end, beside diet and drug therapy, considerable discussion about and some adjustment in the "way of life" may be necessary. One must learn as much as possible about the factors known to produce anginal attacks in the individual patient, e.g., walking distance, size of meal, emotional situations, cold weather, hot weather, speed of walking, stair climbing, insufficient rest, length of working day, etc. Modifications of these factors should be attempted since they may act, much like the stress tests, to induce anginal attacks. Gold (1) lists the following circumstances which influence the daily course of angina pain: (1) spontaneous variations in the course of the pain, (2) changes in the weather; (3) a change of occupation or amount of work, (4) changes of diet, (5) changes in eating habits with increase in the amount of rest before and after meals, (6) condition of the bowels, (7) emotional stress, (8) a change in domestic affairs, (9) confidence aroused in treatment, (10) encouragement afforded by any new procedure, and (11) a change of medical adviser

As indicated in Chapter I, no special diet other than that necessary to reduce weight is indicated (Tables 9 and 10) Such a diet is usually high in protein and low in cholesterol and fat and satisfies many of the criteria for a low cholesterol-low-fat diet. Katz and Stamler (2) have emphasized the life-span pattern of the diet as being of more probable import in relation to atherosclerosis. It is not yet known whether or not the patient with coronary atherosclerosis and effort angina has already reached the point of no return in relation to dietotherapy and possibility of reversal or amelioration of the atherosclerotic process in the coronary vessels.

Obesity *per se* (2a, 2b, 2c, 2f, 2g) has not been established as an etiologic factor in coronary artery disease even though pathologic association has been made (2e) between obesity and the incidence of coronary artery disease Keys (2f, 2g) clinically did not find his coronary patients to be particularly fat However, the existence of obesity in the arteriosclerotic cardiac reduces work tolerance and cardiac reserve (2c, 2d) and reduction in weight is attended with an improvement in these factors.

is advocated with an attempt to limit the number of cigarettes or to substitute alcohol for tobacco.

The patient with angina of effort may play golf, garden or partake in some other form of exercise where sudden bursts of continued exertion is not needed. Vacations should be spaced during the year. Flying (10) is permitted especially in modern pressurized cabins. Where heart failure has occurred or is possible, it is wise to inform the airline to have an oxygen tank available in the plane.

Drugs and other therapy useful and said to be useful in the treatment of effort angina are covered in this chapter Surgical therapy for intractable angina is discussed in Chapter V It is my opinion that sublingual nitroglycerin remains the drug of choice for the treatment of the acute paroxysm of angina and that prophylactic use of the drug, in doses of 0 1 to 0.4 mg. sublingually on an hourly or every two hour basis, should be considered. Where intractable angina or angina decubitus ensues, I consider therapy in the following order: (1) mercurials for the relief of overt or hidden pulmonary congestion, (2) local block therapy (procaine infiltration or ethyl chloride spray) directed at trigger areas of the chest muscles, (3) radioactive iodine therapy or paravertebral block, and (4) finally, cardiopericardiopexy, in one modification or another. In my experience, the numbers of patients with coronary artery disease who need come to surgery for intractable angina are few The disappointment, in general, with the surgical treatment of coronary artery disease has stimulated the need for primary medical therapy directed at the atherosclerotic lesion itself.

DRUG THERAPY

The difficulties in assessing the value of drug therapy in relieving cardiac pain is a product of the limitations in quantitative methods of analysis and the numerous factors other than drug therapy that influence the pain (1, 11, 12) Through many years of experience testing drugs for their usefulness in effort angina (1, 11-18) we have concluded, as expressed by Travell (12), that the method for testing new drugs should include· (1) a representative sample of patients, (2) a matching placebo to evaluate that part of the drug response due to the specific pharmacologic action of the "unknown", (3) either each patient acting as his own placebo control or comparable groups of patients receiving drug and placebo, (4) allocation of patients to drug and placebo groups solely by chance, (5) the double-blind method to eliminate unconscious bias in the results, (6) protection of the patient-participant from possible toxic effects of the drug; (7) suitable criteria of drug action, (8) an effective plan of drug administration and measurement of the effect, (9) simplified recording of data; (10) utilization of all data in the analysis, and (11) application of statis-

previous administration of dihydroergotamine, a *sympatholytic agent. It* is postulated that nicotine may act on the coronary arteries also through stimulation of the posterior pituitary and the release of pitressin, a known coronary vaso-constrictor. More positive effects have been reported (6, 7) for tobacco on the peripheral vascular circulation than on the coronary circulation. Some interdict tobacco entirely (8, 9) in patients with coronary artery disease. My attitude based on present knowledge is as follows: Cigarets are forbidden in the tobacco sensitive group and in patients with concomitant peripheral vascular disease. In others, a modified program

TABLE 10

1500 CALORIE DIET

Food	*Weight*	*Measure*	C	P	F
Breakfast					
Fruit	100 gm	1 serving	15		
Egg	50 gm	1 medium		7	5
Bread or equivalent	30 gm	1 slice	15	3	
Butter	5 gm	1 teaspoon			4
Milk	200 gm	6 oz	10	6	8
Coffee					
Dinner					
Soup, clear					
Meat or equivalent*	90 gm	3 oz		21	15
Vegetable*	100 gm	½ cup	7	2	
Salad					
Bread or equivalent	60 gm	2 slices	30	6	
Fruit	100 gm.	1 serving	15		
Tea					
Supper					
Meat or equivalent*	60 gm	2 oz		14	10
Vegetable*	100 gm	½ cup	7	2	
Salad					
Bread or equivalent	30 gm	1 slice	15	3	
Butter	5 gm	1 teaspoon			4
Fruit	100 gm	1 serving	15		
Milk	200 gm	6 oz	10	6	8
Coffee					
Night Feeding					
Milk	200 gm	6 oz	10	6	8
Soda crackers	*12 gm*	2	10	2	
Totals			159	78	62

*Approximate Composition***

	Unit	*Amount*		*Unit*	*Amount*
Calories		*1500*	*Vitamin A*	I.U	21,000
Carbohydrate	gm	160	Thiamine	mg	1
Protein	gm	80	Riboflavin	mg	1.9
Fat	gm	60	Niacin	mg	12
Calcium	gm.	1	Ascorbic Acid	mg	125
Iron	mg	12			

* Cooked

** This diet is adequate according to the Recommended Daily Dietary Allowances of 1948 (From Diet Manual, Beth Israel Hospital, New York, N.Y.)

found an increase in cardiac output per minute, systolic output and heart rate with no change in blood pressure Their findings suggested that nitroglycerin relieves the pain of angina by increasing the coronary flow relatively more than the work of the heart On occasion (29), a paradoxic action of amyl nitrite, when inhaled by coronary patients, may occur, that is, the cardiac work may be increased above the level of coronary flow and electrocardiographic changes typical of coronary insufficiency may ensue.

PREPARATIONS AND DOSAGE: (1) Amyl nitrite in pearls containing 0.2 cc; (2) tablets of glyceryl trinitrate (nitroglycerin), 0 6 mg, (3) octyl nitrite, 2 cc put up in inhaler form (37); (4) sodium nitrite, 15 to 60 mg. every 3 to 4 hours, (5) erythrol tetranitrate, 30 to 60 mg every 3 to 4 hours. Action begins in fifteen minutes and lasts from 3 to 4 hours (6) Mannitol hexanitrate, 15 to 60 mg. every 4 to 6 hours Action begins in 15 to 30 minutes and lasts from 4 to 6 hours (7) Triethanolamine trinitrate (metamine) 2 mg four times daily (30-32) (8) Pentaerythritol tetranitrate (Peritrate), 10 to 20 mg three times daily (20, 33-35) (9) Nitroglyn 6 mg (gr 1/10), 2 4 mg (gr. 1/25); one pill daily (35a)

SIDE REACTIONS The nitrites may cause flushing, headache, throbbing, palpitation and cardiovascular collapse Mannitol hexanitrate may also cause methemoglobinemia, a rise in intra-ocular pressure or an increase in intracranial pressure

COMMENT The nitrites are the drugs of choice in combatting acute pain of effort angina. The quick-acting nitrites (amyl nitrite and glyceryl trinitrate) are used as diagnostic drugs to differentiate the pain of angina pectoris from other causes of chest pain This, however, also has its pitfalls for Gold (1) has shown that many patients obtain equal relief with placebos placed under the tongue as with glyceryl trinitrate. Studies have also been made (30-36) on the prophylactic use of longer-acting nitrites in angina pectoris The general consensus with use of erythrol tetranitrate or mannitol hexanitrate is that no great advantage is to be found over treating the individual attack As for metamine and peritrate, two groups of investigators (32, 33) have found these no better than a placebo in preventing angina and others (20, 30, 34, 35) have attributed evidence for the efficacy of the drugs based on exercise-electrocardiograph studies and on clinical evaluation Gold (38) has pointed out that the frequent use of nitrites will neither lead to dependence on them or reduce their efficacy

2. Xanthines: In 1895, while working with diuretics, Askanazy (39) noted that theobromine sodio-salicylate, besides its diuretic action, was also useful for pain in angina pectoris

PHARMACOLOGIC BASIS. There is ample experimental evidence to prove that xanthines are coronary vasodilators (40-42). Fowler, Hurevitz and

tical checks to establish the validity of the sampling and the probability of error

The availability of (1) a satisfactory method, as outlined, for testing new drugs and for comparing one agent with another in a reasonably short period of time, and (2) a team of physicians specially trained in the management of patients for pharmacologic investigation and in research methods will go a long way to insure that a decision concerning the therapeutic value of a drug will not be reversed by future studies

The technics for evaluating drug efficacy in effort angina vary from the report card system (14) to the use of exercise alone (13) or exercise and the electrocardiogram (19-21). Using the last mentioned method, Russek and his co-workers (20 and 21) found only glyceryl trinitrate, papaverine and pentaerythritol tetranitrate to be effective as coronary vasodilators in the following doses for the listed drugs·

Drug	*Dosage*
Glyceryl trinitrate	1/100-1/150 grain
Papaverine	1-2 grains I V
Ethyl alcohol	3-8 grains orally
Pentaerythritol (Pentrate)	1.5 grains orally
tetranitrate	1-2 oz
Aminophylline	10-20 mg
Roniacol (betapyridyl-	7 5 grains I V
carbinol tartrate)	6 grains orally
Visammin (Khellin)	100 mg orally
Octyl nitrite	200 mg I M or orally
Tolazoline (Priscoline)	1-4 inhalations
hydrochloride	25-50 mg I M or orally
Tetraethylammonium chloride	300-500 mg I M
Dioxylline (Paveril)	200-500 mg orally
Heparin	50-100 mg I V
Bishydroxycoumarin (Dicumarol)	200 mg
Morphine	¼ grains subcutaneously

CORONARY VASODILATORS

1. Nitrites: Brunton (22) reported on the use of amyl nitrite in angina pectoris in 1867, "on pouring from five to ten drops of the nitrite on a cloth and giving it to the patient to inhale, the physiological action took place in from about thirty to sixty seconds, and simultaneously with the flushing of the face the pain completely disappeared and generally does not return till its wonted time next day" In 1879, Murrell (23) indicated that equally successful results could be obtained with nitroglycerin (glyceryl trinitrate) Bradbury (24) introduced erythrol tetranitrate in 1895

Pharmacologic Basis: Use of nitrites in the relief of pain of angina pectoris depends on their relaxation of coronary vascular tree (25). Coronary vasodilatation outlasts the effects of nitrites on other vascular beds and coronary blood flow is increased despite the concomitant fall in aortic pressure. The nitrites increase coronary arterial blood flow (26-28). Wegria studied the effect of 0 6 mg of nitroglycerin in ten normal persons and

Smith (43) studied the effects of aminophylline on experimentally-induced cardiac infarcts in dogs. They found the infarcted area considerably less in the aminophylline-treated dogs than in the controls and concluded that the theophylline-ethylenediamine was capable of developing collateral coronary circulation in the dog Gold, Travell and Modell (44) repeated this work in cats and measured the size of the infarcts with a planimeter. They could not confirm the results of Fowler.

Preparations and Dosage Clinical studies in angina pectoris have been made with theobromine (0 3 to 0.6 gm. four times a day), theobromine sodio-acetate (0 45 to 0.7 gm., four times a day); theobromine sodio-salicylate (0 5 to 0 7 gm. four times a day), theophylline (0 1 to 0 25 gm. four times a day); theophylline sodio-acetate (0 2 to 0 3 gm four times a day) and theophylline-ethylenediamine (aminophylline) (0.1 to 0 2 gm four to six times a day) (Table 11)

Side Actions: The main disadvantage of oral administration of xanthines is occasional gastric irritation. Intravenous administration may produce giddiness, excitement, faintness, flushing, tingling of lips, collapse and death

Comment: The original enthusiasm for use of xanthines orally in angina pectoris (45, 46, 50, 51) was followed by discouraging reports (1, 48, 49). Finally in 1943 in a review for the Council of Pharmacy of The American Medical Association, Boyer (52), concluded that "the clinical evaluation of the usefulness of the xanthines in the treatment of coronary artery disease is far from satisfactory It seems wise to place the burden of proof on those who claim therapeutic efficacy"

Because of the discouraging results with oral administration of aminophylline, we investigated its usefulness in angina of effort by intravenous administration (13) It was found that an intravenous injection of 0 24 gm. of aminophylline increases the capacity for effort without pain in patients with angina for one hour or more. It is obvious, however, that this method of administration is of limited practical value

3. **Papaverine:** Pal (53) in 1913 first advocated the use of papaverine in treatment of angina pectoris

Pharmacologic Basis. Macht (54) found papaverine to be a powerful dilator of the coronary arteries of frogs The studies of Essex (55) in dogs further corroborated the coronary vasodilator action of papaverine

Preparations and Dosage Papaverine hydrochloride is given orally in doses of either 33, 100 or 200 mg four times daily This intravenous dose is 65 to 100 mg Ethaverine (ethyl analogue of papaverine) (56, 57, 154) is given as 50 mg. capsules, two to four times daily Dioxyline phosphate (paveril) is administered in doses of 200 mg, one to six times daily (20, 58, 59).

TABLE 11

EFFECT OF ORAL XANTHINES USED IN ANGINA PECTORIS

Author and Reference	*Theobromine*	*Theobrom Sodio-Acetate*	*Theobrom Sodio-Salicylate*	*Theobrom Calcium Salicylate*	*Theophylline*	*Theophylline Sodio-Acetate*	*Theophylline Ethylene Diamine (Aminophylline)*	*Choline Theophyllinate*	Result
Gold *et al.* (1)	0 3 gm (1 to 4 gm O D)						0 1 gm (0 6 to 0 8 gm O D)		Poor
Gilbert & Kerr (45)	0 3 gm 4 i d	0 7 gm 4 i d.	0 7 gm 4 i d	0 5-0 7 gm 4 i d	0 1 gm 4 i d	0 3 gm 4 i d	0 1-0 2 gm 4 i d		Good
Riseman (19)	0 5 gm 4 i d	0.5 gm 4 i d.	0 5 gm 4 i d	1 0 gm 4 i d	0 25 gm 4 i d	0 2 gm 4 i d	0 2 gm 4 i d		Mixed
Musser (46)							0 1-0 2 gm t i d		Good
Williams *et al* (47)	0 45 gm 4 i d. 0 90 gm. t i d					0 18 gm 4 i d 0 36 gm t i d	0 2 gm t i d		Fair
Master *et al* (48)	0 45-0 6 gm 4-6 i d						0 2 gm 4-6 i d		Poor
Evans & Hoyle (49)			1 gm. t i d				0 2-0 3 gm t i d		Poor
LeRoy (50)							0 2 gm. t i d		Good
Massel (51)			0 3 gm q i d	0 5 gm q i d			0 1 gm. q i d		Good especially with phenobarbital
Batterman (153)								0 05 to 0 1 gm 3 to 4 daily	Good

action in dulling response to pain rather than its coronary vasodilator action (70).

5. **Khellin (Visammin):** Khellin is an active principle of the fruit Ammi Visnaga, known in Arabic as "Khella" It was first isolated in a purified form in 1930, although it was first extracted in 1879. Chemically, it is a dimenthoxymethyl-furano-chromone.

PHARMACOLOGIC ACTION: Khellin is a dilator of the coronary blood vessels (71) and is active in a minimal concentration of 10^{-6} It has produced significant increases in coronary blood flow in both intact animals and in the dog's heart-lung preparation

PREPARATION AND DOSAGE: Khellin is administered in oral doses of 50 mg. to 100 mg. three times daily (72, 73). The intramuscular dose is 100 mg. to 200 mg.

SIDE ACTIONS. Oral administration may produce nausea, insomnia, constipation, dyspepsia, and a sensation of warmth.

COMMENTS The Egyptian group (74, 75) treated 250 patients with angina pectoris with oral doses of 50 mg to 100 mg. three times daily. The duration of observation and treatment varied from 3 months to 2 years with response to treatment occurring after from three to ten days depending on the severity of the angina. Occasionally, intramuscular doses of 100 to 200 mg. were given. Fifty-six per cent of the patients showed good improvement. There were no control studies excepting that when a placebo was substituted for the active drug, the attacks recurred

Rosenman, Fishman and Katz (76) have indicated that controlled studies with placebo and khellin revealed no benefit in some patients and dramatic responses occurred in others as manifested by a decrease in the number of attacks of precordial oppression and in the number of nitroglycerin tablets used (73). Others have reported beneficial effects with khellin (77-79).

Greiner and his co-workers (14) studied the effects of khellin in 39 patients who, in alternating courses, were also given tablets of a placebo of sugar of milk, which resembled the active drug in size, shape and color The khellin was administered in doses of 100 to 150 mg daily A comparison of approximately 1,500 days administration of each of the two agents showed that khellin had no greater affect than sugar of milk in the control of the pain of angina of effort. These negative findings were confirmed by Hultgren (80).

6. **Tetraethylammonium Chloride:** The use of this drug in angina pectoris has been advocated by Christy (81) and Hirshleifer (82). Christy (81) treated 10 patients with the anginal syndrome with a bi-weekly intramuscular injection of tetraethylammonium chloride in doses ranging from 200 to 800 mg. per injection for periods of at least 1 year. Of the 10

SIDE ACTIONS. Papaverine may cause dizziness, nausea, vomiting, drowsiness, auriculoventricular and intraventricular block, cardiac arrest, premature beats, coupling, ventricular tachycardia and fibrillation.

COMMENT: There is diverse opinion as to the efficacy of oral doses of papaverine for relief of angina pectoris. Pal (60) and Boehm (61), Macht (54) and Katz and Elek (62) report (60) favorable effects in angina pectoris. Pal and Macht gave their doses intravenously (30 to 40 mg). Boehm and Katz and Elek gave their medication orally, the latter investigators in doses of 100 mg. four times daily. Gray, Riseman and Stearns (63) also found the drug of value for pain in coronary insufficiency and coronary thrombosis when given intravenously in doses of 65 or 100 mg They found, however, that oral doses of 33, 100 or 200 mg four times daily for 1 week were of little value in clinical treatment of angina pectoris

This same mixed feeling was expressed by Gold (64) in a timely review of the value of papaverine in coronary artery disease. He believed that it had some value but how much was still in doubt. Its administration was not without dangers. These included toxic rhythms, namely, premature beats, coupled rhythm, ventricular tachycardia and partial A-V block, all of which may occur with doses within the therapeutic range. The value of the blind test was demonstrated again by Katz and his co-workers (65) who re-evaluated the status of papaverine in angina pectoris They had previously reported favorable results with the drug (62). This group studied 13 patients in the following manner: no medication was given during a 6-week adjustment period, then placebo capsules identical in appearance with papaverine was given for at least 4 weeks, then capsules of papaverine hydrochloride containing 100 mg were substituted blindly and given orally in doses of from 400 to 800 mg. daily. The authors now concluded that papaverine administered orally in these doses was in general of limited value in angina pectoris Ethaverine (55) was reported to have no value for angina With pavenil there are mixed opinions as to its efficacy (20, 57, 58).

4. Ethyl Alcohol: This is a commonly used remedy for angina attacks. Its use is based on the the concept that it is a vasodilator. However, Dixon (66) found experimentally only slight vasodilation of the coronary arteries. Evans and Hoyle (67) found that objectively only 1 in 11 patients was able to do more work following phophylactic use of brandy. Stearns *et al.* (68) found that therapeutic doses of whiskey (1 ounce) did not measurably shorten the duration of attacks of angina pectoris or increase the capacity of the patient for work. Eggleston (69), however, recommends a small drink of brandy or whiskey to relieve the pain of angina pectoris.

The effects of alcohol in relief of angina must be attributed to its central

by Graham and his co-workers (91). This finding was incidental to an investigation of the effects of heparin on the concentration of the serum lipoproteins (S_f 12-20 and 20-100). Efficacy of heparin in effort angina has since been reported by Engelberg (92), while, on the other hand, no significant benefits were found by Russek (93), by Miller, Zinn and Griffith (94), by Rinzler *et al.* (95), by Binder (96), Chandler and Mann (97) and Port (98).

A comparison of the levels of serum lipoproteins of the Sp 12-20 and Sp 20-100 classes in our study (95, 99) showed no significant change in concentration after 6 weeks of heparin or placebo administration. This finding was confirmed by Chandler and Mann (97).

2. Androgens: The basis for use of androgens in the treatment of angina pectoris was the finding of Edwards, Hamilton and Duntley by spectro-

TABLE 12

EFFECT OF INTRAMUSCULAR TESTOSTERONE PROPIONATE IN ANGINA PECTORIS

Author and Reference	*No of Cases*	*Dosage*	*Results*
Walker (101)	9 [illegible]	25 mg four times in first week [illegible]	Improvement in 7 cases
Hamm (102)		[illegible] injections—30 in 1 year)	
Sigler & Tulgan (103)	20 (all M)	25 mg two times weekly	In 11—marked relief In 5—some relief In 4—none
Strong & Wallace (104)	15 (all M)	25 mg every 4 to 5 days, totalling 12 injections	In 5—marked improvement In 7—slight improvement In 3—none
Waldman (105)	10 (all M)	25 mg two times weekly	In 7—favorable [illegible]
Lesser (106)	100 (92 M) (8 F)	25 [illegible] 2 [illegible] jec [illegible] injections	[illegible]
Levine & Likoff (107)	19 (16 M) (3 F)	25 mg three times weekly for 4 weeks	In 5—marked relief In 1—moderate relief In 2—questionable relief In 11—none
Riseman (108)		25 mg daily	No value
Levine & Sellers (109)	21	25 mg two to three times weekly	In 2—marked improvement In 4—moderate improvement In 4—slight improvement In 11—none
Summers (110)	67 (58 M) (9 F)	25 mg five times weekly for 6 weeks	In 9—marked improvement In 34—moderate to slight improvement In 24—none

patients, 2 had complete relief, 5 considerable improvement, 2 no relief, and 1 patient could not be followed adequately. No blind testing was applied in this study

Israel (82a), in a survey of the usefulness of tetraethylammonium chloride for the relief of chest pain, cites an instance of a 42-year-old man with acute myocardial infarction and agonizing precordial pain in whom 300 mg of tetraethylammonium chloride injected intravenously produced immediate and permanent relief of pain after 25 mg. of morphine subcutaneously and 15 mg. intravenously had failed to be of any benefit.

Despite these results, because of its known hypotensive effects and because of the *possibility of inducing myocardial infarction, this drug* is to be used with caution in patients with coronary artery disease (83, 84).

MISCELLANEOUS AGENTS

1. Heparin: The steps by which heparin came to be used in the treatment of effort angina were as follows: It was first demonstrated that heparin abolishes alimentary lipemia (85-90). Secondly, while investigating the relationship between atherosclerosis and serum lipoproteins of the S_f 10-100 class in rabbits, the California Group showed that the daily injection of heparin for 3 to 8 weeks prevented atherosclerosis and suppressed the development of molecules of the S_f 10-50 class. Subsequently these findings were applied to man and it was observed (91) that the intravenous injection of a single dose of 100 mg. of sodium heparin in a patient with a myocardial infarction and a high level of serum lipoproteins of the S_f 10-20 and 20-100 classes caused a prompt shift of the lipoprotein molecules from the higher to the lower S_f classes This was an acute effect which reverted to the initial pattern within 24 hours Graham *et al* (91) then administered heparin intravenously to 20 patients at intervals of 2 to 14 days. These investigators noted that "*a small proportion of the patients showed depressed in S_f 10-20* levels which persisted for the full 3 to 14-day intervals between intravenous injections of heparin, but in general the levels observed 3 to 14 days after injection showed no average trend toward reduction." They stated, on the other hand, that they had "direct evidence that with a suitable heparin dosage schedule, chronic lowering of the serum S_f 10-20 levels can be obtained." To substantiate this 1 patient is desscribed who for 1 month maintained an S_f 10-20 depression for the 3-day intervals between heparin injections (100 mg. each) and on cessation of the heparin injections showed a slow, progressive rise over a 1-month period to a level which approached the original S_f 10-20 concentration A second patient is mentioned who received 100 mg of heparin by vein daily for 4 weeks and showed a similar effect.

Dosage: Sodium heparin, 100 mg. twice weekly intravenously.

Comment: Relief of angina pectoris by heparin was first reported in 1951

claims have been disputed by many groups of investigators (15, 16, 114-120).

In our investigation (15, 16), 41 patients with chronic chest pain and with arteriosclerotic and/or hypertensive heart disease were selected at random from the Cardiac Clinic. Three patients failed to finish the full course of therapy so that we had to analyze 38 patients, 19 having received synthetic alphatocopherol and 19 a matching placebo Seventy-six per cent of the patients had effort angina alone; the remainder exhibited mixed types of cardiac and somatic chest pain.

Because of the possible carry-over effects of alpha-tocopherol, the blind-test method for investigation selected was that of matching groups Therefore, the patients were paired and matched as closely as possible with respect to sex, age, cardiovascular status, duration and type of chest pain, presence of hypertension, history of previous myocardial infarction, presence of abnormal electrocardiograms, and such miscellaneous data as the presence of somatic pain syndromes, osteoarthritis of the spine, diabetes mellitus and anemia. There was a resulting close correlation in the percentages of clinical abnormalities between the groups.

Synthetic alpha-tocopherol was given by mouth in daily doses of 200 mg for about 2 weeks, and thereafter, 300 mg A similar number of matching placebo tablets was given The average duration of administration of the vitamin was 16 weeks (10-20 weeks) and of the placebo, 16 6 weeks (10-20 weeks) According to the criteria for dosage and duration of medication set up by Shute, Shute and Vogelsang (112), the periods of 2 5 to 5 months, during which our patients received "optimum" doses of alpha-tocopherol, represented adequate time for clinical trial

The response to medication was essentially the same for the alpha-tocopherol and for the placebo groups Thus, no improvement was noted in 12 treated subjects (63 per cent) and in 14 controls (73 per cent) Subjective improvement was reported by seven treated patients (37 per cent) and by 5 controls (27 per cent). These figures relating to improvement are in accord with the observations of Evans and Hoyle (49) who showed that the administration of a placebo to patients with angina pectoris was accompanied by a diminution of pain in 37.5 per cent of their 66 cases

We concluded that alpha-tocopherol was not of appreciable benefit in treatment of angina pectoris.

4. **Cytochrome C:** Cytochrome C acts by enhancing the tissue uptake of oxygen For this reason Proger (121) has used this in patients with myocardial anoxia. Cytochrome C, 60 mg intravenously, has been shown to prevent anoxic changes in the electrocardiogram of cardiac patients brought on by breathing a 10 per cent oxygen mixture. They, therefore, recommended its use in angina pectoris.

We tested the effect of intravenous cytochrome C on the chest pain in patients with effort angina (17) by the following method. The patient was

photometric studies that the diminished arterial supply to the skin of castrated men was increased after administration of testosterone propionate (100).

Dosages: A dose of 25 mg. of testosterone propionate intramuscularly twice weekly seems to be the average dose. Frequency of medication and duration varies with different investigators (Table III).

Side Actions: Testosterone therapy can cause marked sodium chloride and water retention and on occasion may precipitate cardiac failure (109).

Comment: The majority of investigators (101-106) reports some degree of improvement in the pain of angina pectoris under therapy with testosterone propionate (Table 12). Riseman (108), Levine and Likoff (107), and Levine and Sellers (109) give an unfavorable report Lesser (106) attributes this lack of success to insufficient treatment since about one-third of his group showed no noticeable improvement during the first month of therapy In Lesser's study also the possible psychologic effect of injection therapy *per se* was eliminated by giving 5 patients 6 consecutive injections of sterile sesame oil prior to receiving testosterone propionate None of the patients on sesame oil showed any appreciable change in symptoms while progressive improvement occurred in the same patients following use of hormone therapy Sigler and Tulgan (103) also used this technic. However, the study was not an entirely blind one. In both instances the physician knew when he had given a placebo. This may have prejudiced his questioning of the patient Other than this criticism one must remember that testosterone propionate therapy is costly and must be given parenterally Summers (110) has shown that even the small group of patients (9 of 67 cases) who at first noted considerable improvement in the frequency and the severity of the anginal attacks, reverted within a few months to that which had been present before treatment was begun. Forty-one per cent (5 of 12 patients of the control group treated with sesame oil also reported improvement.

There is no adequate explanation for the apparent efficacy of androgen therapy in angina pectoris Waldman (105) has postulated that testosterone may act in a number of ways by vasodilatation of the coronary arteries, by development of a collateral circulation; by correction of an androgen deficiency or by an improved cardiac muscle metabolism of phosphorus and creatine The use of testosterone must be further questioned because of its known ability to shift lipoproteins toward the atherosclerotic-like side (111).

3. Vitamin E: The stimulus for the use of vitamin E in angina pectoris was given by three Canadian physicians (112, 113) who noted some improvement of the "anginal pain" in 96 per cent of 84 patients on dosages of vitamin E (in terms of alpha-tocopherol) ranging from 150 to 600 mg. daily with a usual dose of 200 mg to 300 mg. daily Improvement commenced in approximately 5 to 14 days after the onset of medication These

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being the decrease in the "anoxiating" effect of adrenalin on the heart muscle by an abolition of the abnormal irritability of the adrenal secretory mechanism In addition to the adrenal treatment 57 per cent of these patients were also given irradiation over the upper thoracic and cervical spine

McMillan and his co-workers (134, 135) irradiated the adrenal glands of 23 patients with severe angina pectoris. Each adrenal area received 600 r in three divided doses a week. Thirteen patients were greatly relieved, 4 moderately, 3 slightly and 3 not at all These patients were observed for a period of from 2 to 12 months The treatment did not alter the life expectancy

Our interest in the use of radiation therapy to the spine in the treatment of angina pectoris was aroused by the report of Sussman (136) who indicated that sub-erythema doses of roentgen radiation to the lower cervical and upper thoracic spine to include the sympathetic ganglia was able to improve the severity of angina pectoris in 11 of 16 subjects so treated We investigated this problem (137) by means of the blind-test method previously described and could not confirm the observation.

Twenty-nine ambulatory patients with heart disease (hypertensive and/or arteriosclerotic), chronic chest pain and spinal osteoarthritis were divided into two groups matched with respect to age, sex, cardiovascular status, duration and type of chest pain and degree of osteoarthritis of the spine. Of these, 55 per cent had effort angina alone, 28 per cent had both effort angina and somatic chest pain; and 17 per cent had only somatic chest pain One group (14 patients) was chosen blindly by the x-ray therapist to receive cervical and dorsal irradiation in doses of 200 r twice weekly for 3 weeks. The control group (15 patients) received a placebo course of similar x-ray treatments, that is, these patients went through the exact routine for preparation for x-ray as the others, except that no roentgen radiation was given.

The patients were followed in our Cardiac Clinic for at least 12 weeks after completion of x-ray therapy. Since the x-ray therapist had designated which group should receive true and which placebo exposure, we were unaware of the nature of the exposure in any particular case. Furthermore, the designation of the group was not revealed until the clinical data had been analyzed. Our results showed no significant difference in the response of treated and control groups. Thus, chest pain was not improved in 13 of the treated patients (93 per cent) and 11 of the controls (74 per cent). Partial improvement was reported by one treated patient and four controls

7. **Mercurials:** Gold (138) has stressed the value of dehydration with mercurials to control the cardiac pain occurring at rest This has been verified by Soloff (139).

These patients do not have congestion in the lungs in the usual sense, that is, rales cannot be heard, but their symptoms improve when the weight is decreased by mercurialization Gold summarizes "Not all patients respond,

walked back and forth over a standard set of steps until the onset of his usual type of chest pain. The rate of walking was set by the subject himself and at any subsequent time on the same subject, he was kept at the same rate Each test with cytochrome C was coupled with a control test on the same day, thus eliminating the effect of spontaneous variations in pain on different days in the same subject. Cytochrome C was used intravenously in doses of 50 mg in 5 cubic centimeters of solution. Physiologic saline was used as the control solution Five minutes after the injection, the patient was walked, then rested for an hour, then given the second injection, and walked again.

We were unable to demonstrate any increase in the capacity for effort without pain in patients with angina pectoris following intravenous injection of cytochrome C as compared with a placebo injection of physiologic saline solution.

5. *Thioureas:* Encouraging results have been reported with their use for angina pectoris (122-128) According to Raab (129, 130), thiouracil exerts a "heart protecting" effect by suppressing the formation of thyroid hormones. *His further thesis is as follows: Sympathetic stimulation* (exercise, emotion, etc.) is accompanied by an acute influx of the adreno-sympathogenic catecholamines, nor-epinephrine and epinephrine, into the myocardium. These catecholamines exert a specific oxygen-wasting chemical effect upon the heart muscle which is in principle independent of cardiac work and which is potentiated by the thyroid hormone Coronary sclerosis exaggerates the resulting myocardial hypoxia to a painful maximum (angina pectoris) Nitrites and the thioureas act by decreasing the metabolic pain-producing effectiveness of these catecholamines. Garb (131), on the other hand, found that the isolated papillary muscle of the cat soaked in nitroglycerin or sodium nitrite showed no block in the effects of the amines either on contractile force, automaticity or electric potentials.

Successful results have been reported with the use of thiouracil in doses *of 0.4 to 0 6 gm. daily for 3 weeks followed by a daily maintenance* dose of 0.2 gm. propylthiouracil in daily doses of 75 to 125 mg and methylthiouracil in initial doses of 400 to 500 mg daily followed by maintenance doses of 100 to 200 mg. daily.

DiPalma and MaGovern (132) caution that as the basal metabolic rate is lowered by thiouracil there is a tendency for water retention to occur so that pulmonary edema and increased dyspnea appear. They further show that those patients who benefit mostly from thiouracil administration have an elevated basal metabolic rate before treatment. They conclude that this is the only indication for use of the drug other than as a therapeutic test in selection *for thyroidectomy in those patients with angina pectoris.*

6. Radiation Therapy: Raab (133) was able to improve the anginal attacks in 76 per cent of 200 patients by radiation of the adrenals, the rationale

tients who developed extrasystoles just before the onset of pain brought on experimentally by peddling on a stationary bicycle with a fixed load at a fixed speed. Quinidine sulfate was given in doses up to 0 1 gm. four times a day. One patient was able to do twice as much exercise before pain developed and no irregularities were noted in the pulse before, during, or after exercise.

Our impression is that quinidine should not be used in the routine treatment of angina pectoris *per se* except where arrhythmias might interfere primarily with myocardial efficiency and secondarily with coronary sufficiency (147-149).

12. **Radioactive Iodine:** Radioactive iodine provides a means for performing a chemical thyroidectomy. Such a procedure is advocated for the somewhat less than 5 per cent of patients who remain disabled from angina pectoris or congestive heart failure despite all medical measures (150). This method of treatment lowers the total metabolism of the body and so reduces systemic circulatory needs to the extent that the needs of the body and the cardiac reserve match more closely. The drug is given to euthyroid patients as evaluated clinically, and by basal metabolism, serum cholesterol, serum protein bound iodine and thyroid uptake of I^{131} Blumgart (150) reported on 1,070 patients so treated. The cases were gathered from 49 cooperating clinics and so represents results in many hands. Of 720 patients with angina pectoris, of whom 200 also had evidences of congestive heart failure, 76 per cent showed worth-while improvement (40 per cent excellent and 36 per cent good) Of 350 patients with congestive heart failure, 62 per cent showed worth-while improvement (32 per cent excellent and 39 per cent good).

An excellent result (150) denotes that the patient is markedly improved over pretreatment status, with either no recurrence of symptoms or a marked decrease in the frequency and severity of angina pectoris or congestive failure, despite markedly increased activity. A good or worth-while result denotes definite improvement with a decrease in frequency and severity of attacks of angina pectoris or congestive failure on the same amount of activity as before treatment.

The dose schedule as reported in 1950 (151) included a total dose varying from 25 5 to 176 millicuries (average 61 0). Affective dosage may result from a single dose of 25 5 to 42.5 millicuries (average 31 5) or up to 6 doses may be needed.

The program of I^{131} treatment is given by Blumgart, Freedberg and Kurland (152) as follows·* "In every instance tracer doses of 100 to 150 microcuries of I^{131} by the thyroid is measured by the direct counting technic. This measurement is made 24 hours, 48 hours, 72 hours and 96 hours

* Courtesy of Dr Blumgart and the *New England Journal of Medicine.*

but some do in a dramatic way. I have the impression that the pain in those patients who also have exertional dyspnea or nocturnal dyspnea is more apt to respond well. Because of a clear cut relationship between the relief of dyspnea and the pain by dehydration in some cases which have both symptoms, I am inclined to think that in some cases cardiac pain is the sole clinical manifestation of left heart failure. If you treat them as cases of left heart failure, their capacity for exertion without pain is enhanced and nocturnal pain may either lessen or vanish"

8. **Cobra Venom:** Freedberg and Riseman (140) found that administration of cobra venom to patients with angina pectoris increased the standardized exercise tolerance in 7 of 12 patients studied. Since in these patients medication did not prevent the electrocardiographic changes associated with exertion, they concluded that the action was not one of coronary vasodilation The dose was 10 mouse units three times the first day, followed by one injection daily for 7 days and then biweekly injections of the same dose

9. **Nicotinic Acid:** Stokes (141) reports no improvement from oral administration of nicotinic acid (200 mg daily) or nicotinamide (200 to 400 mg. daily) either in prevention or relief of angina

10. **Digitalis:** Gilbert and Fenn (142) reported that digitalis exerts a vasoconstrictor effect. The administration of digitalis might therefore be thought to increase the pain in angina pectoris However, Gold (143) found no increase in cardiac pain in 120 patients with effort angina given digitalis even in toxic doses. They concluded that digitalis does not exert any direct constrictor effect on the coronary arteries in patients with coronary artery disease.

11. **Quinidine:** Freedberg, Riseman and Spiegl (144) using the exercise tolerance method, tested the effect of quinidine sulfate on the capacity for work without pain in patients with angina pectoris. The tests with quinidine sulfate were carried out after administering 0.3 gm. of the drug four times daily for 1 week, with an additional dose 1 to 2 hours before the exercise. Twelve patients were studied Four showed a marked response, 5, a moderate response and 3, no response. A marked response indicated an increase of over 50 per cent in the work capacity without pain as compared with the pre-medication status. A moderate response indicated some increase over the control level by not over 50 per cent

The value of quinidine sulfate led to an investigation of other cinchona alkaloids (145). Quinidine, quinine, cinchonadine and cinchamindine were found to decrease the frequency of attacks of angina and increased the exercise tolerance. Quinine sulfate (0.3 to 0.4 gm. every eight hours) appeared to be the drug of choice from the standpoint of availability and low toxicity as well as effectiveness

Proger *et al* (146) found an increase for capacity for work without pain when cardiac irregularities were abolished by quinidine. There were 2 pa-

mas apparently then begin to function and may be affected by subsequent doses of I^{131}. Subsequent doses frequently lead to tenderness and gradual disappearance of the nodule, the induction of myxedema with its characteristic clinical manifestations, rise in serum cholesterol and lowering of the basal metabolic rate.

"The first clinical intimations of incipient hypothyroidism may consist of one or more of the following. slight fullness or puffiness of the face, increased sensitivity to cold, slight stiffness of the joints or arthralgia and parasthesias Concomitantly, the patients usually report that the attacks of angina are milder or less frequent or that dyspnea and orthopnea are diminished It has been our practice to permit marked hypothyroidism or, in some instances, even complete myxedema to develop, in order to assure ourselves that all thyroid tissue has been affected, and then to give 6 or 12 mg. of thyroid daily. In each patient thyroid dosage must be adjusted to maintain him at the lowest metabolic level at which he experiences the maximum relief from his cardiac disease and the minimum discomfort from myxedema. In certain cases this may not be possible, the patient showing little or no improvement over his pretreatment status when sufficient thyroid is administered to obviate the discomfort Most patients are maintained at a level of approximately -20 to -25 per cent on a daily dosage of 6 to 30 mg. of thyroid.

"Occasionally patients may suffer a recurrence of their symptoms because residual thyroid tissue has regenerated with return of the metabolic rate to pretreatment levels. In such instances, thyroid is withdrawn, and after tracer doses show adequate uptake of I^{131} an additional therapeutic dose is administered.

"In addition to these special considerations, the same careful supervision and therapeutic program indicated for all patients with heart disease is essential"

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after the administration of I^{131} by mouth. From these data the biologic half-life is estimated and the equivalent dosage in roentgens delivered to the thyroid is calculated. As a check on this, the urinary excretion of I^{131} is also measured for each of the 3 days following the administration of I^{131} by mouth Assuming that the normal thyroid weighs 25 to 30 gm., the initial dose is calculated to deliver approximately 30,000 to 50,000 equivalent roentgens. Since the average euthyroid 24-hour uptake is approximately 30 per cent and is turned over with an average biologic half-life of 7 days, the initial dose of I^{131} is approximately 30 mc.

"After the administration of the therapeutic dose, similar measurements are made by direct counting of the uptake of the dose by the thyroid 24, 48 and 72 hours after its administration to ascertain the amount of the therapeutic dose retained in the thyroid

"During the next few weeks the patient is observed closely. During this period and later, we have made numerous observations of possible toxic effects and of the occurrence or absence of thyroiditis. We have observed the ambulatory patients three times weekly for 2 weeks. It is, of course, imperative to instruct all patients concerning the safety precautions relative to contamination of clothing and skin, storage of urine immediately after the therapeutic dose and other necessary safeguards Approximately two thirds of the patients have exhibited mild to moderate thyroiditis lasting 1 to 10 days It has been severe in only one instance No treatment except the use of analgesics has been indicated Inasmuch as thyroid hormone is apparently released during the stage of thyroiditis, the activities of the patient should be reduced to a minimum during this time

"After the first 2 weeks the patient is seen by us at 1 to 2-week intervals, at which time serum-cholesterol, basal metabolic rate and other measurements are made, in addition to a clinical appraisal of his condition Careful inquiry in regard to early signs of hypometabolism is made. In our experience hypometabolism has developed 5 weeks to 6 months after an adequate dose of I^{131} When patients do not develop hypometabolism within several months, it has been our practice to administer additional doses after preliminary tracer dose studies to determine whether residual tissue capable of taking up I^{131} exists The average number of doses per patient was 2 3, but more than 3 doses of I^{131} were necessary for 6 patients As many as 4 5 or even 6 doses at various periods of time have proved to be necessary, but in each case myxedema was finally achieved.

"Repeated administration of I^{131} is particularly indicated when thyroid adenomas are present In some patients these adenomas are plainly evident at the time of initial examination. In other patients they have become apparent only after the normal thyroid has disappeared after the first 1 or 2 doses of I^{131}. Presumably these nodules are initially non-functioning and do not take up I^{131} until the normal thyroid tissue has been destroyed. The adeno-

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There are three methods of revascularization used (4, 5). The first consisted of grafting tissues upon the heart in order to establish vascular communications between the coronary arteries and the arteries of the engrafted tissues. This is called extracoronary anastomosis. The tissues that have been used for this purpose include the parietal pericardium, mediastinal fat, lung, skeletal muscle from the chest wall and omentum brought up through an opening in the diaphragm (6-10). This method in general has proved disappointing

The second method of revascularization involved the use of agents for the purpose of producing an inflammatory reaction between the heart and parietal pericardium (11, 12). One can make effective intercoronary connections by abrading the surface of the heart and rubbing a mildly irritating substance such as powdered asbestos, 0 2 gm, on the surface. In 1943, Feil (13) summarized the clinical experiences with the Beck procedure which is the combination of pectoral muscle grafts and cardiopericardial adhesions with asbestos Thirty-seven patients with coronary sclerosis and angina pectoris were operated upon with an operative mortality of 37 8 per cent Nine patients died 4 months to 6 years after the operation Of 23 operative survivors, 14 (60 9 per cent) had excellent results, 5 (21.7 per cent) had good results and 4 (17 4 per cent) had little or no improvement.

Thompson and his co-workers (2, 14-16) use the following technic for cardiopericardiopexy as a one-stage surgical procedure The operation takes place in three steps. Step 1 includes placing the patient in the supine position, making a small cutaneous incision over the left fifth costal cartilage and carrying it laterally along this cartilage to a length of about 7 or 8 cm, exposing the costal cartilage, and excising a 5 cm segment of the cartilage. Step 2 exposes the anterior mediastinum, including the pericardium. In step 3 the pericardium is opened, the sac is explored, 2 to 4 drams (56 7 to 113.4 gm), by volume, of sterile dry magnesium silicate powder (U S P talc) are spread over the anterior surface of the heart and around its borders, and the surgical wound is closed. The operation can be completed in 30 minutes or less

The foreign body reaction, which is invoked by the talc introduced into the pericardial sac, reflects itself in a rise of temperature and involves the lungs, pleura, heart, pericardium, and mediastinum. The temperature may rise as high as 104°F (40°C) and subsides gradually within 10 days Pulmonary consolidation in the form of interstitial pneumonitis begins after the first operative day, but the patient is not dyspneic or cyanotic The mediastinitis that makes its appearance from the first postoperative day is demonstrable roentgenographically by bulging mediastinal outlines and gradually resolves Extensive adhesions form between the myocardium and the pericardium, but the adhesive granulomatous pericarditis that has

CHAPTER V

Surgical Therapy

"SURGICAL therapy of angina pectoris should be reserved for patients who, after adequate observation, cannot be controlled by medical means" (1). Such surgery now has centered about two methods of attack: (1) creating new channels of blood supply, and (2) interruption of sensory pathways It is to be remembered that in interpreting the statistical results of surgery that the surgeon is usually dealing with patients with either severe paroxysmal chest pain or intractable angina decubitus in whom medical therapy has been unavailing.

Revascularization of the Heart: The various procedures described for augmenting the blood supply of the heart are designed for three main purposes: (1) to alleviate pain, (2) to protect against subsequent myocardial infarction, and (3) to bring the myocardium "the good red blood" which may prevent the fatal ventricular arrhythmias attendant upon ventricular muscle ischemia (mechanism death) Since pain is a subjective response and since all surgical series have been analyzed without a parallel control group, attention has also been directed at the size and patency of the newly created anastomotic channels as evidence of efficacy of the revascularizing procedure.

Blumgart and Paul (2) have pointed out that the post-operative demonstration of fine communications between the heart and surrounding structures by colored watery solutions or India ink is of little import because such fine communications are of no immediate functional significance for they do not protect the myocardium from infarction if a coronary artery is occluded suddenly. In truth, in the presence of coronary narrowing or occlusions, intercoronary anastomoses which will permit a lead-agar mass *to penetrate to vessels 40 micra in diameter or more in fixed sections* are abundant and always present, on the other hand, vessels of this caliber exist in only 15 per cent of normal human hearts In fact, Blumgart (2) adds, these vessels in coronary artery disease are so abundant that it is difficult to conceive how surgery can further increase their size. It has been known that the development of such a basket-weave of collateral channels has been nature's way of treating a disease for which physicians have as yet no specific therapy

Nevertheless, Thompson and Plachta (3) have indicated that a study of vessels within the granulomatous pericarditis produced by magnesium trisilicate crystals revealed internal diameters far above the critical 40 micra even 10 years after human cardiopericardiopexy.

zation by the use of phenol as one of the steps in the surgical treatment of angina pectoris. From their experiments on dogs, *removal of the epicardium* of the dog's heart with 95 per cent phenol permitted anastomoses between pericardial vessels and the coronary arteries that were large enough to carry the Schlesinger mass (40 micra or larger) In humans, phenolization was combined with the installation of talc and the application of the lingula of the lung to the denuded myocardium. The total operating time in 18 patients with intractable angina ranged from 11 to 26 minutes There were no operative deaths The operation is reported to result in consistent relief of pain. All but 4 had complete relief of pain. Two patients died within 2 months of the operation from fresh coronary occlusion after having been completely relieved of their anginal pain The first patient was operated upon in December, 1951, and he was still alive and working at the time of their report.

Arterialization of the cardiac veins was first suggested as a third method of revascularization of an ischemic myocardium by Roberts, Browne, and Roberts (20) in 1943. They created an arteriovenous anastomosis in dogs between an aortic branch and the coronary sinus by means of a glass cannula, and then ligated the coronary artery Chicago blue dye injected into the sinus was found in the capillaries Later, experiments on dogs using a systemic artery-coronary sinus anastomosis were carried out by Senstrom (21) and Beck (22) These experimental trials led Beck to attempt this method in humans (23)

It is to be remembered that the excellent test of benefit of the anastomosis from the aorta to the coronary series in dogs in whom the coronary artery was later ligated may not be directly applicable to man because the coronary arterial tree of man and dog differ (24) in that large anastomosis between the left anterior descending and left circumflex and right coronary occur frequently in the dog This makes for difficulty in interpretation of effects of single artery ligation in the dog

Beck and Leighninger (25, 25a) have performed two types of revascularization operations

(1) The Beck I *procedure consists of partial ligation of the coronary* sinus, abrasion of the surface of the heart, application of 0 2 gm of powdered asbestos as an inflammatory agent, and grafting of partial pericardium and mediastinal fat to the raw surface of the heart This is a one-stage procedure and provides intercoronary arterial communications, elevation of coronary sinus pressure, and extracoronary communications.

(2) The Beck II procedure consists of grafting a vein between the aorta and the coronary sinus in the first stage and three weeks later the sinus is partially ligated *to 2 to 3 mm near its ostium*

The Beck I procedure, carried out on 33 patients and evaluated 3 months

been established is a benign, beneficial, and permanent sequela that is directly responsible for the increase in maintenance of myocardial vascularity (16, 16a).

Over a period of 14 years (1938 to 1951), Thompson has performed this operation on 57 patients. The operative and hospital mortality was 12 per cent Of the 50 remaining patients followed to 1951 or their time of death, 37 were men and 13, women. The age range was 35 to 68 years with an average of 51 years Thirty-three patients were still living by 1951. The shortest duration of symptoms before operation was 3 months, the longest 15 years with an average of 3½ years. The living patients had had their symptoms for an average of 2¾ years, while the patients who died had theirs an average of 4½ years. The shortest length of life after the operation was 2 months, the longest 13¾ years with an average of 5 years. Four tests were used to determine postoperative benefits: (1) the decrease in amount of anginal pain; (2) the increase in exercise tolerance; (3) the improved ability to attend to daily needs, and (4) a return to the former or some other gainful occupation Using these criteria as a guide, those with 50 per cent improvement were classified as poor results, 50 to 75 per cent improvement, moderate, and with more than 75 per cent improvement, marked. The results in 50 patients are as follows: 5 (10 per cent) are classed as poor results, 25 (50 per cent), moderate; and 20 (40 per cent), marked.

Of 17 patients followed to their death, the average duration of symptoms before operation was 4½ years and the average span of life after operation was 5 years. Thompson considers this 9½ years span in excess of the average span of life of 4 to 5 years of the coronary patient from the onset of symptoms. Sigler (18) also indicated an average length of survival of his group who died to be 4.6 years However, Block (19) found the 5-year survival rate to be 58 4 per cent of his series and the 10-year survival to be 37 1 per cent after onset of symptoms This survival rate of 37 1 per cent in the non-operated cases compares closely with the 9½-year survival rate of 17 of 50 patients (34 per cent) operated by Thompson. One must not lose sight, however, of at least the subjective deterioration of Thompson's patients, all of whom had severe angina when operated upon.

Dack and Gorelik (17) reviewed their results on cardiopericardiopexy performed in 36 patients who were partially or completely incapacitated by coronary insufficiency or congestive heart failure The immediate operative mortality was 5.5 per cent In a follow-up period ranging from 3 to 42 months, over three-fourths of the patients exhibited good or excellent clinical improvement as manifested by decreased angina pectoris, increased exercise tolerance, and ability to return to work

Harken, Black, Dickson, and Wilson (85) have advocated de-epicardiali-

have done well Seven of the 9 patients who were incapacitated before the operation were working. Three had slight pain on severe exertion, and 5 were completely free of pain. There was 1 failure among the 9 survivors: The patient still had pain as severe as before the operation. It would seem that the internal mammary artery was placed in the heart without sufficient slack to allow for the movement of respiration This artery was probably firmly thrombosed. Of the 3 patients who were in status anginosis before the operation, 2 died 60 to 62 hours, respectively, after the operation, and 1 died of cardiac arrest on the operating table. One of the nine surviving patients had had coronary occlusion since the operation, without infarction. This patient had returned to work, and it appears that his mammary artery implant probably protected him from death and definitely protected him from infarction.

Ligation of the Great Cardiac Vein: Experimental attempts to induce the development of a collateral circulation through the intramyocardial channels which empty into the channels of the heart by cardiac vein ligation alone preceded those of arteriolization of the cardiac veins heretofore discussed Coronary sinus ligation was subjected to thorough study (29-32). The mortality rate in dogs after coronary sinus ligation has varied with different investigators.

Further, the studies of Thornton and Gregg (33) indicated that though the coronary sinus pressure may rise immediately after its ligation, this pressure is not maintained and after 30 days it returns to normal The immediate effects of coronary sinus occlusion in dogs included cyanosis of the left ventricle, occasional petechial hemorrhages and larger extravasations under the epicardium It has also been found that congestive effects are lessened as the site of the sinus obstruction moves to the left and that ligation of the great cardiac vein practically never results in gross congestion of the left ventricle (21).

For this last reason and because of the high experimental mortality produced by ligation of the coronary sinus in the dog found by Gross, Blum and Silverman (30) and by himself (31), Fauteux (34) believed that ligation of the great cardiac vein in humans would provide adequate collateral circulation and a lower operative mortality His results of 40 cases of angina pectoris treated by great cardiac vein ligation (34-36, 37) show an operative mortality of 20 per cent with 6 subsequent deaths and benefit from the operation in 72 per cent of the 40 cases Nineteen of the surviving 26 patients became free of symptoms and were able to return to their former work The addition of pericoronary neurectomy to the ligation of the great cardiac vein has been performed by Fauteux (36, 37) He, however, is unable to assess properly the value of this combination operation over a ligation of the great cardiac vein alone

to about 5 years postoperatively, resulted in an improvement in 84.8 per cent of these patients, no change in 9.1 per cent and more pain in 6 1 per cent. Seventy-eight per cent of the patients were better able to work, with about 27 per cent with no limitations and 51.4 per cent with some.

The Beck II procedure carried out on 43 patients and similarly followed as above, resulted in an improvement of 88 4 per cent of these patients, no change in 7 0 per cent and more pain in 4 6 per cent. In 79 1 per cent of these patients, the ability to work was improved, 41.9 per cent with no limitations and 37.2 per cent with some limitation. In a 3-year period from 1951 through 1953, there were 108 operations with an operative mortality of 2.8 per cent due to thoracotomy alone, 7 5 per cent from the Beck I procedure and 26 1 per cent from the Beck II operation. In the first 6 months of 1954, there were 27 operations with an operative mortality of 3 7 per cent from thoracotomy alone, 4 per cent from the Beck I procedure and 0.0 per cent from the Beck II procedure The late mortality (2½ months to 5 years) from all causes in 106 cases was 9.4 per cent in the Beck I and 11.3 per cent in the Beck II procedure. In November, 1954, Beck expressed a preference for the Beck I procedure (25)

Bailey *et al.* (26) has indicated that the ideal patient for arterialization of the coronary sinus is 50 years of age or younger, has had a single myocardial infarct more than 6 months before, has a normal blood pressure and heart size and is suffering from angina decubitus or uses many nitroglycerin tablets The major contra-indications include. recent myocardial infarction (within 6 months), congestive heart failure, gallop rhythm, a blood pressure of 180/100 mm. Hg. or higher, a heart size increased beyond 10 per cent of predicted value, age over 55 years, and a calcified aorta

Vineberg (27) showed that experimentally in dogs anastomoses could be induced between the coronary vessels and an internal mammary artery transplanted into the myocardium of the left ventricle The presence of communications between the implanted artery and the circulation of the left coronary vessel was studied by means of x-ray examination of the injected specimens, serial sections through the sites of anastomoses and by making plastic casts of the arteries involved to show the nature of the anastomoses Internal mammary artery implantation was performed by Vineberg (28) in 12 men between the ages of 36 and 57 years with coronary artery insufficiency Nine of the 12 patients had no angina at rest, and 3 were in status anginosus All were unable to work at the time of the operation. Their periods of disability varied from 7 to 36 months Ten of the 12 patients had one or more proved myocardial infarction Of these 12 patients, 9 survived. All survivors did not have angina at rest, before the operation Even though 2 of these patients had had both anterior and posterior infarctions, there was still some myocardial muscle left to revascularize Both

Saccomano, Utterback and Klemme (45) have suggested that surgical removal or alcohol injection of the second, third and fourth thoracic sympathetic ganglia on the affected side only will alleviate angina pain. This is based on experiments upon dogs in which stimulation of C_8 and T_1, when isolated, produced no effect on the heart rate or blood pressure. The effect on pulse rate was most marked on stimulating the second and third nerves with diminishing effect on the fourth and fifth thoracic nerves The effect on systemic blood pressure was more or less constant from the second thoracic nerve down to the seventh thoracic nerve.

1. Paravertebral Block with Alcohol: Paravertebral alcohol block was introduced by Swetlow (42) as a method of obtaining more prolonged anesthetic effects than were possible with block of the upper thoracic sympathetic ganglia by procaine hydrochloride Levy and Moore in 1931 (46) summarized the reported cases of angina pectoris treated with paravertebral alcohol block and added 9 cases of their own. In 1941 (47), they reported their complete results with an additional 36 patients. The technic used was that described by White and Smithwick (48). Of Levy and Moore's total of 45 cases, 4 died within 3 weeks of the block, and 1 was lost to follow-up

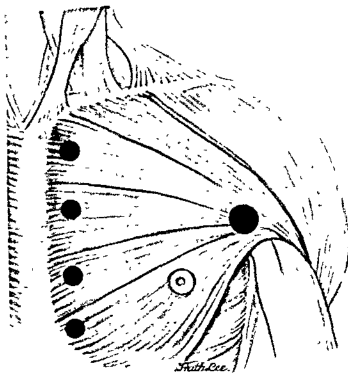


Fig 25 Common sites of trigger areas in chest muscles Pectoralis major

INTERRUPTING SENSORY PATHWAYS

William Harvey left the impression that the heart was devoid of pain sensation because, on touching, pricking or pinching the heart of a patient who, through a childhood accident, had been left with an exposed heart, no painful response was elicited. It is reasonable that proper stimulus for eliciting pain was not used. In 1899, François-Franck (38) offered a suggestion that sympathectomy would relieve anginal pain. However, it was not until April 2, 1916, that the Rumanian surgeon, Jonnesco (38a) performed the first cervical sympathectomy for the relief of the pain of angina pectoris Although the operation was left-sided only, the operation was dramatically successful in relieving the chest pain. During the next 10 years, studies by Fontaine (38b), by Cutler (38c), and Porter and Richardson (39), using the technic of cervical sympathectomy, showed that less than 2 out of 3 patients were being relieved of their pain At this point in medical progress, two contributions were being made in relation to cardiac pain Firstly, the thoracic cardiac nerves were demonstrated by the anatomists (40). At the same time, Mandl (41) and Swetlow (42) were elaborating on the value of paravertebral block with procaine and alcohol, respectively, in the treatment of cardiac pain.

In 1933, White, Garrey and Atkins (43), using a method for producing cardiac pain in dogs described by Sutton and Lueth (44), made some experimental and clinical observations on cardiac innervation. A fine silk ligature, threaded on a curved needle, was passed just beneath the uppermost portion of the descending branch of the left coronary artery and its accompanying veins This was brought out through a glass tube and the wall of the chest was sutured in several layers around it to obtain an air-tight closure. Traction on the thread for a few seconds produced a characteristic stiffening of the limbs, marked increase in the rate and depth of respiration, and, if maintained for over 10 or 15 seconds, a definite restlessness on the part of the animal Respiratory changes were recorded on a kymograph and were used as a graphic method of recording painful stimuli.

As a result of these experiments, it was shown that cardiac pain was not transmitted by the vagus nerves since cutting both vagi did not eliminate the sensation of pain. Bilateral resection of both stellate ganglia diminished but did not block all sensory stimuli from the heart. Bilateral removal of the sympathetic ganglia from the stellate down through the fourth thoracic ganglion or section of the upper five posterior dorsal nerve roots appeared to interrupt all sensation from the heart From these experiments, they concluded that for the routine treatment of angina pectoris, paravertebral injection of alcohol into the upper four to five thoracic ganglia and their rami is the surgical method of choice

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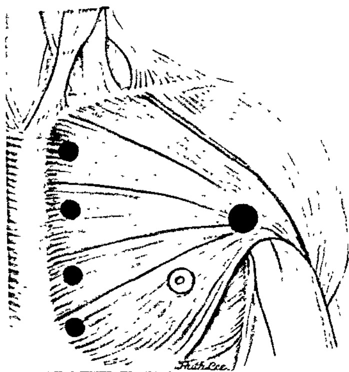


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INTERRUPTING SENSORY PATHWAYS

William Harvey left the impression that the heart was devoid of pain sensation because, on touching, pricking or pinching the heart of a patient who, through a childhood accident, had been left with an exposed heart, no painful response was elicited. It is reasonable that proper stimulus for eliciting pain was not used. In 1899, François-Franck (38) offered a suggestion that sympathectomy would relieve anginal pain. However, it was not until April 2, 1916, that the Rumanian surgeon, Jonnesco (38a) performed the first cervical sympathectomy for the relief of the pain of angina pectoris. Although the operation was left-sided only, the operation was dramatically successful in relieving the chest pain. During the next 10 years, studies by Fontaine (38b), by Cutler (38c), and Porter and Richardson (39), using the technic of cervical sympathectomy, showed that less than 2 out of 3 patients were being relieved of their pain. At this point in medical progress, two contributions were being made in relation to cardiac pain. *Firstly*, the thoracic cardiac nerves were demonstrated by the anatomists (40). At the same time, Mandl (41) and Swetlow (42) were elaborating on the value of paravertebral block with procaine and alcohol, respectively, in the treatment of cardiac pain.

In 1933, White, Garrey and Atkins (43), using a method for producing cardiac pain in dogs described by Sutton and Lueth (44), made some experimental and clinical observations on cardiac innervation A fine silk ligature, threaded on a curved needle, was passed just beneath the uppermost portion of the descending branch of the left coronary artery and its accompanying veins This was brought out through a glass tube and the wall of the chest was sutured in several layers around it to obtain an air-tight closure. Traction on the thread for a few seconds produced a characteristic stiffening of the limbs, marked increase in the rate and depth of respiration, and, if maintained for over 10 or 15 seconds, a definite restlessness on the part of the animal. Respiratory changes were recorded on a kymograph and were used as a graphic method of recording painful stimuli

As a result of these experiments, it was shown that cardiac pain was not transmitted by the vagus nerves since cutting both vagi did not eliminate the sensation of pain. Bilateral resection of both stellate ganglia diminished but did not block all sensory stimuli from the heart Bilateral removal of the sympathetic ganglia from the stellate down through the fourth thoracic ganglion or section of the upper five posterior dorsal nerve roots appeared to interrupt all sensation from the heart. From these experiments, they concluded that for the routine treatment of angina pectoris, paravertebral injection of alcohol into the upper four to five thoracic ganglia and their rami is the surgical method of choice.

has perfected an x-ray technic to insure greater accuracy in the placement of needles (1). Since paravertebral block with alcohol must be performed without anesthesia in order to observe the occurrence of Horner's sign and a hot, dry hand, some degree of discomfort and nervousness may occur and this may precipitate fatal myocardial infarction.

2. **Stellate Ganglionectomy and Four Upper Thoracic Ganglionectomy:** Because of the above objections to the paravertebral block with alcohol, wherever possible, ganglionectomy is performed (50). White (1) states that it is the operation of choice at the Massachusetts General Hospital Olivecrona (50a) in Sweden treated 71 patients by this technic In 44 per cent there was complete relief from pain In 41 per cent it converted severe forms of angina pectoris into milder types. Unsatisfactory results were obtained in 7 per cent. Eight per cent of the 71 patients died within 1 month

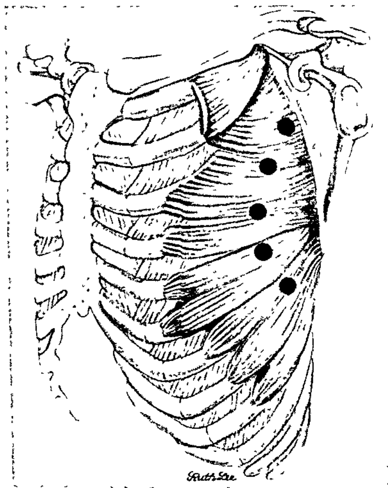


Fig 27 Common sites of trigger areas in chest muscles Serratus anterior

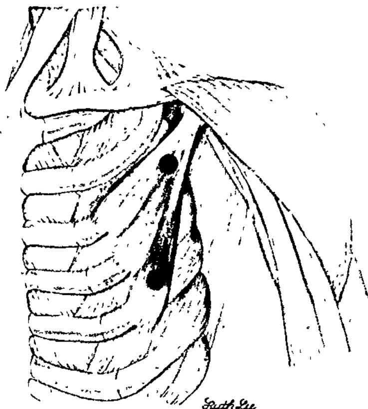


Fig 26 Common sites of trigger areas in chest muscles Pectoralis minor

examination. Of the remaining 40 cases, relief was obtained in 31 (77.5 per cent). In 19 patients, (47 5 per cent) the relief was marked and permanent. In 9 patients, (22 5 per cent) no relief was obtained. In this series there was a high percentage of neuritides following the procedure since 38 patients were so affected. In other reported results (1, 49) this complication was reduced to between 10 and 30 per cent.

In 1948, James White (1) reported his experience with this method on 75 patients. Fifty-six were completely or nearly completely relieved of their pain on the side of injection In 21.3 per cent, there were fair results, that is, the intractable angina was so reduced that the patient was relatively comfortable with routine medical measures without narcotics Eight per cent died as a direct result of the procedure and there were failures in another 8 per cent. In the later years of the report, with the improvement of the injection technic, the proportion of good results has increased steadily, so that the results in the latter third of the series are distinctly the best. The last death was in the fifty-eighth case.

One of the objections to this technic lies in the fact that it is a blind procedure The needle may enter the pleura or the subarachnoid space. White

if sympathectomy was extended high enough into the anginal pathway (stellate ganglion plus second, third and fourth thoracic ganglia). Best results were obtained in a further series (52) in patients who had complete resection of the anginal pathway (the first to the fourth thoracic ganglion) bilaterally. This procedure is therefore recommended in the severe hypertensive with anginal pain.

Fish and Grantham (53) were able to immediately relieve the pain in the initial stage of an acute posterior wall infarction by procaine block of the left stellate ganglion

3. Posterior Rhizotomy: Posterior rhizotomy involves the division of the non-myelinated axon of the peripheral sensory ganglion According to White (1) the advantages of the procedure lie in the fact that the technic of laminectomy and posterior root section is a standard procedure which can be carried out by the average neurological surgeon There is no chance of nerve regeneration and rhizotomy on both sides can be done at a single

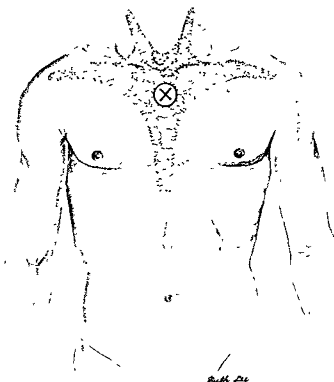


Fig 29 Common sites of trigger areas and the distribution of referred pain from these muscles Trigger areas anterior to the sternum in the rudimentary sternalis muscle give rise to a reference of pain which may extend up and down from the base of the neck to the epigastrium.

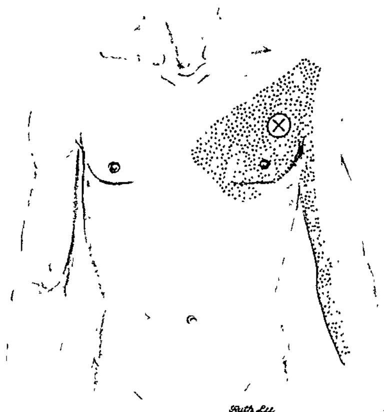


Fig. 28 Common sites of trigger areas and the distribution of the referred pain from these muscles Trigger areas in the lateral part of the precordium, where the *pectoralis major and minor muscles overlap, give rise to pain widely distributed over* the precordium, occasionally to the scapula and frequently to the medial epicondyle of the elbow and ulnar distribution of the forearm and hand

of the operation, 2 of these occurring during the operation The most serious medical complication is myocardial infarction during or after the operation. This occurred in 10 cases; in 5 it led to their death. In 18 patients (25 per cent), "migration of pain" occurred, that is, accentuation in the non-operated side of a discomfort of which the patient had not been previously aware. After bilateral operations, the pain in some of these patients migrated to the neck, jaws or temples. This pain appeared on exertion and was relieved by nitrites.

Evans and Poppen (51, 52) became interested in the possibility of relieving anginal pain in patients undergoing splanchnicectomy who had severe hypertension and angina pectoris. In a series of such patients (51), they were able to show that the incidence of relief of associated anginal pain was related to the level of resection of the sympathectomy, that satisfactory relief from anginal pain could be obtained in 100 per cent of such patients

dyspnea and movement of the left foreleg) when tridirectional tension in one plane was applied to the coronary vessels in such a manner as to cause no damage in blood flow.

Lian *et al.* (56) has used both pre-aortic plexus block and resection for the treatment of angina pectoris. They believe that physiologically the interruption of these sensory pathways effects a sympathectomy of all cardiac elements in the cervical sympathetic trunk Novocaine infiltration is done every other day for a total series of 6 to 8 treatments and a maintenance infiltration may be carried out every eighth, tenth ord fifteenth day Injury to the aorta or brachial plexus must be avoided. Nineteen of their patients had a pre-aortic plexus resection Thei pratients have been followed for 18 months. Two died of myocardial infarction 4 and 27 days after operation. Sixteen patients have had a complete disappearance of pain.

5. ***Local Block Therapy:*** *The myofascial genesis of chest pain has been*

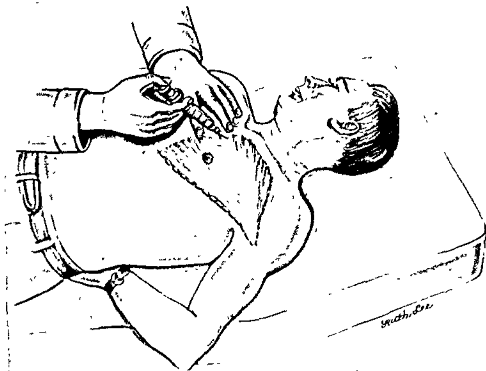


Fig 31 Technic for procaine infiltration One to four cc. of procaine hydrochloride in physiologic saline in concentrations of from 0 25 to 0 5 per cent is used for each trigger area A 1 to 1½-inch (24 gauge) or a 2-inch (23 gauge) needle is used depending upon the site of the trigger area and the musculature of the patient The positioning of the patient as shown is important so that the muscles may be placed on the stretch in order to make the finding and the infiltration of trigger areas easier. Pectoralis major

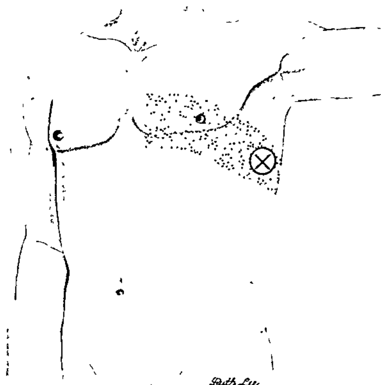


Fig 30 Common sites of trigger areas and the distribution of referred pain from these muscles. Trigger areas in the axillary region in the serratus anterior muscle induce a spread of pain at the corresponding level which travels anteriorly almost to the sternal border and posteriorly as far as the interscapular line, and occasionally to the volar aspect of the arm as far as the palm

operation However, (1, 49) it is a time-consuming procedure and a severe operation for cardiacs. A bilateral root section involves the risk of a subsequent transverse myelitis. There is also sensory loss of areas of the chest supplied by the cut nerves.

Ray (49) has performed 11 operations with 1 death on the second postoperative day due to coronary occlusion. Another patient died 3 weeks after operation, while up and about, of a coronary occlusion. Ray concludes that "the patients are not rehabilitated completely and there are disadvantages to almost any method. But from the standpoint of rational procedure in properly chosen cases I think that it has value."

4. **Pre-Aortic Plexus Block:** In 1942, Wenckebach (54) postulated that sudden distention of the aorta stimulated the nerve plexus in the adventitia and produced cardiac pain. This idea was extended by Martin and Gorham (55) who obtained typical pain response in dogs (increase in heart rate,



Fig 33 Technic for procaine infiltration of serratus anterior.

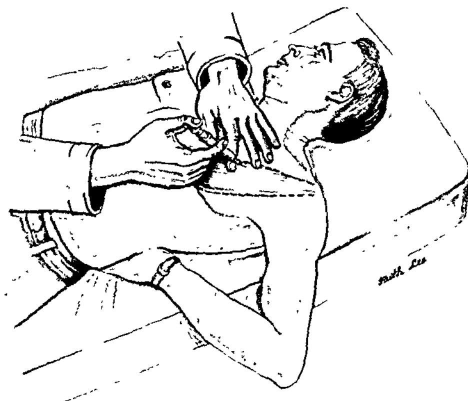


Fig 32 Technic for procaine infiltration of pectoralis minor

discussed in the chapter on differential diagnosis. Muscle spasm sufficient to cause chest pain may also result from reflex effects of visceral disease which in the instance of the heart is referred to as the somatic component of cardiac pain Such reflex visceromotor phenomena following coronary artery spasm or closure give rise to spasm of the chest muscles, tenderness (physically diagnosed by the presence of trigger areas) (Figs. 25-27) and pain (4, 5, 57-69a). This is similar to the reflex spasm of the abdominal musculature in an acute surgical condition of the abdomen Further, this secondary spasm of the chest muscles may develop into a vicious cycle which may exist without further dependence on stimuli from the heart and may, in turn, establish areas of referred pain (Figs. 28-30). Pain in the chest, whether of primary visceral origin or secondary somatic origin, is a source of anxiety and emotional conflict to the patient and therapy must be directed at one as thoroughly as at the other Procaine infiltration of the trigger areas (Figs. 31-33) or spraying with a rapidly volatile cooling agent (Fig 34), such as ethyl chloride, of the skin surface overlying the trigger area are effective methods for treating the somatic component of cardiac pain (50, 57-60, 64, 69).

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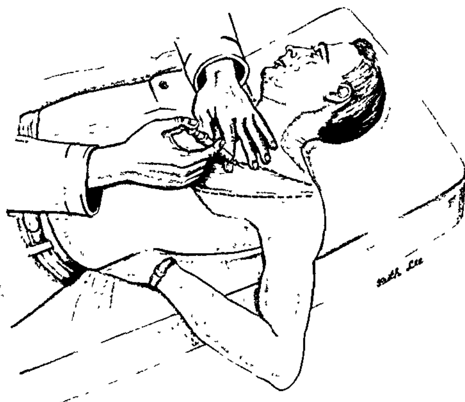


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marked *correlation of positivity of the ergonovine stress test with occlusive* atherosclerosis of the small coronary arteries and myocardial damage (75).

It is necessary to define the abnormal zone of hypersensitivity known as a trigger area. Its essential characteristic is that when it is stimulated by pressure or needling, it gives rise to a brief reference of pain. The referred pain is usually perceived at a distance from the trigger area, but as in the case of precordial muscles, it may circumscribe the trigger area itself. The distribution of pain referred from trigger areas is relatively constant for the site of origin, thus, similarly located trigger areas in different individuals produce similar, and therefore, predictable pain reference patterns Although trigger areas reside occasionally in the skin, they are in most instances located within the myofascial structures. Muscles which

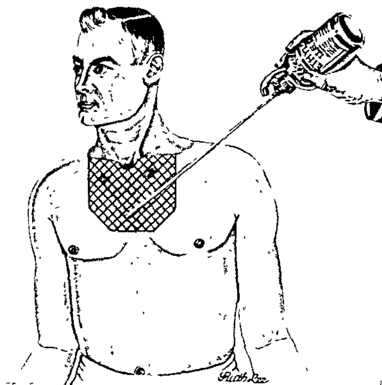


Fig 34 Technic of ethyl chloride spray The container is held 1 to 2 feet away from the skin and is sprayed at an acute angle The spray is applied in even sweeps in a rhythm of a few seconds on and a few seconds off The skin should not be frosted and the rhythmic spraying is continued until tenderness or pain at the trigger area disappears Discontinue if there is no effect within 10 or 15 minutes Be sure to eliminate fire hazards and to elevate the patient's head because of the possible anesthetic effect of the ethyl chloride

The efficacy of procaine cannot be attributed solely to its local anesthetic action, firstly because the relief of pain outlasts the transitory pharmacologic action of the drug, and secondly because dry needling or infiltration with saline will accomplish the same result. Ethyl chloride spray is a form of counter-irritation and counter-irritants applied to the skin have been shown to relieve experimentally induced deep pain (70), with intermittent cold more effective than continuous cold It has also been shown (71) that an interrupted puff of air applied to the frog's skin in a certain manner could produce adaptation The rhythm of stimulation and the angle which the air jet makes with the skin influences the speed of adaptation These experimental studies suggest at least two important features of the mechanism of action of ethyl chloride spray, as we employ it: intermittency of cold and intermittency of touch The initial cold shocks set up a barrage of afferent impulses which is followed by post-stimulatory depression and alterations of the central excitatory state. Another factor in the relief of pain by ethyl chloride spray may be a brief hypesthesia of the skin due to cold which momentarily reduces the stream of afferent cutaneous impulses in phase with the subnormal (post-stimulatory) state of conduction in the central nervous system

To further study the role of rapidly volatile cooling agents and viscerocutaneous mechanisms in cardiac pain, we induced a standardized cardiac pain by means of ergonovine (72-74). We used the Stein ergonovine test as described in Chapter II in cooperative, ambulatory patients with effort angina and normal resting electrocardiograms. We found that ethyl chloride spray could block ergonovine-induced chest pain in these patients with coronary insufficiency when the spray was applied to the reference zones of cardiac pain, either just prior to the injection of ergonovine or subsequently when pain has appeared. In the case of prior application, the spray was directed to the sites where the particular patients experienced pain during effort angina. The results showed that ergonovine angina was often prevented and relieved even though at the same time depression of the S-T segment, typical of ergonovine action in this special test subject occurred. Similar results were obtained when for ethyl chloride, another rapidly cooling spray, namely, a halohydrocarbon mixture which consists of 15 per cent dichlorodifluoromethane and 85 per cent trichloromonofluoromethane, was substituted. We selected this mixture because it is not flammable, not a general anesthetic and is not so disagreeable to the patient in that the initial cold shock of application is less than for ethyl chloride.

We were able further to correlate the positive ergonovine test with clinical evidence of coronary artery disease in man by inducing coronary atherosclerosis in the living rabbit by cholesterol-feeding and then finding a

Previous examination for trigger areas during hospitalization had revealed no trigger areas. Ethyl chloride spray was applied to the chest in interrupted sweeps, with subsidence of pain in a few minutes Physical and electocardiographic examinations at this time revealed no acute cardiovascular changes The patient had no further chest pain until her discharge one month later

Analysis of age, sex, duration of pain before local treatment and other factors was made in this series of 20 cases in relation to the results of therapy. The number of treatments given ranged from 1 to 5, with an average of 2 2 treatments In summary, the results show that these methods for local interruption of myofascial trigger mechanisms (ethyl chloride spray and/or local procaine infiltration) secured complete relief of chest pain in 15 patients (75 per cent), improvement in 2 (10 per cent), and no relief in 3 patients (15 per cent).

An opportunity to study the somatic component of cardiac pain of effort angina presented itself during an investigation of the effect of heparin in effort angina (76) During the control period of 2 months prior to heparin administration, the extent of the somatic component of cardiac pain (57, 58, 62, 77) was evaluated and an attempt was made to eliminate trigger areas in the chest muscles in 16 patients with angina of effort Ethyl chloride spray and procaine infiltration technics were used in a twice weekly basis This type of local block therapy was continued until trigger areas disappeared or until it was apparent that maximum benefits had been achieved The ability of ethyl chloride spray to relieve the somatic element of cardiac pain has been discussed above One patient in this series, for example, averaged 49 nitroglycerin tablets per week during the first five weeks of the control period Coincident with the elimination of the somatic trigger areas his consumption of nitroglycerin decreased and during the ensuing 4 weeks of the control period averaged only 23 tablets per week There is an inherent difficulty in setting up suitable controls for the placebo effect of a physical agent, such as cold, but our impression was that the course of treatment with spray succeeded in making the lives of these patients more comfortable and secured a reduction in the total amount of pain Kennard and Haugen (69a) in mapping trigger areas in the chest muscles of normal subjects and cardiac patients found a higher incidence of trigger areas in patients with heart disease

In about 15 per cent of patients persistent pain develops in the shoulder, arm, wrist or hand after the usual period of recovery from the symptoms of infarction This has recently been termed the shoulder-hand syndrome If it occurs on the left side a problem arises in differential diagnosis between further coronary-artery disease and the syndrome since it is not always associated with progression of coronary disease It is our belief

frequently develop trigger areas in association with coronary artery pain are the pectoralis major, pectoralis minor and the serratus anterior (Figs. 25-27).

Since our initial reports (57, 58, 62) on the efficacy of spray and procaine infiltration in relieving the pain when such treatment is directed at the somatic component of cardiac pain, we have been interested in answering these questions. *Do all patients with a fresh myocardial infarct exhibit* trigger areas in the chest muscles? In what proportion of these patients with myofascial trigger areas does post-infarction chest pain present such a problem that despite the usual potent analgesias, local treatment directed at the somatic component is indicated?

Of 48 patients with acute myocardial infarction, 27 patients (56 per cent) were found to have trigger areas in the chest muscles.

Of the 27 patients with trigger areas, in 7 (25 per cent) the trigger areas were judged to be clinically latent and no local treatment was given.

The remaining 20 patients could be divided into two groups: (1) those *with chest pain which persisted as a complication of the infarction* and which thus presented a problem soon after admission (7 patients); (2) those who developed a recurrence of chest pain during their stay in the hospital some time after the initial pain of the infarction had subsided (15 patients) Two patients had pain of both types and are included in both groups

An example of the first category follows.

G. R., a 38-year-old white male, was admitted to the hospital after 12 hours of substernal pain On admission, his electrocardiogram showed changes diagnostic of acute posterior wall infarction Demerol, 100 mg by muscle every 4 hours, was given At the end of 18 hours in the hospital, the severe chest pain was still present despite 4 doses of demerol. A trigger area was palpated over the lower part of the sternum This was sprayed intermittently *with ethyl chloride, and after a few minutes the pain was relieved com*pletely and did not return during his 6 weeks in the hospital

An example of the second category follows:

E. C. H., a 37-year-old white female, was admitted with chest pain of 13 hours duration The electrocardiogram showed the changes of an acute anterior wall infarction. Chest pain subsided soon after admission, and the course was *uneventful until 7 days later when she was given an enema* (5 P.M.). While on the bed-pan she began to suffer from substernal pain which continued thereafter for about 2 hours, despite large amounts of demerol, 225 mg by muscle. At about 7 P.M., examination of the chest wall revealed a very sensitive trigger area over the upper part of the *sternum*

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that the shoulder-hand syndrome at its onset represents the somatic component of cardiac pain which persists after the initial visceral stimulus is gone. It has been our policy to observe all patients with acute myocardial infarction for pain, limitation of motion, or the presence of trigger areas in the muscles of the shoulder girdle and upper extremity during the course of the disease and to apply the technics of local block described above to forestall the vexatious problem of the shoulder-hand syndrome. This will be further discussed under complications of acute myocardial *infarction*

The Patient With Arteriosclerotic Heart Disease as a Surgical Risk for Operations Other Than Those to Relieve Pain or Heart Failure: Statistical reports (78-83) on this problem deal with the patient with coronary artery disease as one with either arteriosclerotic heart disease alone, as one with healed myocardial infarction or with angina pectoris. Emergency surgery during the first weeks of an acute myocardial infarction is not reported (78-83) but it is known that patients with acute appendicitis have been operated upon during the first week after a coronary thrombosis and have recovered

I shall summarize the statistical findings of surgery in the coronary *artery disease patient by chronological report so that one may ascertain* whether the improvements in technic, anesthesia or therapy for infection may have influenced the mortality rate. The surgical procedures involve all types of major intro-abdominal gastroenterologic, urologic and gynecologic conditions

In 1930, Butler, Feeney and Levine (78) reported a mortality incidence of 3 (7.7 per cent) of 41 operations performed on 35 patients with angina pectoris and of 8 (44 5 per cent) of 20 operations performed on 20 patients with healed myocardial infarction. Brumm and Willius (79), reporting in 1939, operated upon 257 patients with angina pectoris (32 of these also had healed myocardial infarctions) with an operative death rate of 11 *(4.2 per cent).*

Morrison (80) performed 485 operations on 311 patients with arteriosclerosis heart disease (no angina or occulsion) with resultant operative deaths in 72 (14 8 per cent) Thirty-seven operations were done on 25 patients with previous coronary occulsion with 3 (8.1 per cent) deaths, 48 operations were done on 41 patients with angina pectoris with an 8 6 per cent mortality.

Hannigan *et al.* (81) reported the statistics in 1951 on patients operated for cancer. There were 58 patients with electrocardiographic evidence of healed infarction. Twenty-four patients gave a history of previous coronary occlusion. Eight of these also had angina pectoris while 5 of the remaining 34 patients also gave a history of angina There were 3 (5 2 per cent)

operative deaths. The incidence of cardio-respiratory complications was greater in those who had enlarged hearts and who underwent long surgical procedures. The complication incidence was unrelated to age of infarct, angina, hypertension, sex, age or cardiac classification.

De Peyster, Paul and Gilchrist (82) performed 55 operations on 33 patients with a previous myocardial infarction (7 with angina, too) with 15 (27.2 per cent) operative deaths. Lochhead *et al.* (83) reports 3 deaths in 17 patients with 30 operations (10 per cent mortality) in those patients with myocardial infarction and 2 deaths in 15 patients with angina pectoris on whom 21 operations were done (9 4 per cent mortality). Summarizing three series (81-83), Lochhead reports an operative mortality of 6.3 per cent for angina pectoris and 7 2 per cent for myocardial infarction. This is based on the number of operations

Anesthetic Management: Dripps and Vandam (84) state that there is no single satisfactory approach to the anesthetic management of patients with coronary artery disease but they recommend (1) assurance through personal contact that the anesthetist is aware of the patient's particular problem, (2) adequate sedation prior to operation, (3) smooth induction of anesthesia, (4) maintenance of blood pressure, and (5) administration of oxygen They suggest that cyclopropane be avoided in instances where myocardial irritability is known to be increased (patients with arrhythmias), although they have anesthetized many patients with serious cardiac disease with cyclopropane and small amounts of ether Hannigan (81) has reported a 43 per cent incidence of cardio-respiratory complications following the use of pentothal anesthesia. Spinal anesthesia may result in a decrease in peripheral resistence and cardiac output and may result in coronary insufficiency However (84), despite the reduction in coronary artery flow caused by the drop in blood pressure, adequate oxygenation of the myocardium may still be present at the lower blood pressure since the heart needs less oxygen

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The Patient With Arteriosclerotic Heart Disease as a Surgical Risk for Operations Other Than Those to Relieve Pain or Heart Failure: Statistical reports (78-83) on this problem deal with the patient with coronary artery *disease as one with either arteriosclerotic heart disease alone, as one with* healed myocardial infarction or with angina pectoris. Emergency surgery during the first weeks of an acute myocardial infarction is not reported (78-83) but it is known that patients with acute appendicitis have been operated upon during the first week after a coronary thrombosis and have recovered.

I shall summarize the statistical findings of surgery in the coronary artery disease patient by chronological report so that one may ascertain whether the improvements in technic, anesthesia or therapy for infection may have influenced the mortality rate. The surgical procedures involve all types of major intro-abdominal gastroenterologic, urologic and gynecologic conditions.

In 1930, Butler, Feeney and Levine (78) reported a mortality incidence of 3 (7 7 per cent) of 41 operations performed on 35 patients with angina pectoris and of 8 (44.5 per cent) of 20 operations performed on 20 patients with healed myocardial infarction. Brumm and Willius (79), reporting in 1939, operated upon 257 patients with angina pectoris (32 of these also *had healed myocardial infarctions)* with an *operative death rate of* 11 (4 2 per cent)

Morrison (80) performed 485 operations on 311 patients with arteriosclerosis heart disease (no angina or occulsion) with resultant operative deaths in 72 (14 8 per cent). Thirty-seven operations were done on 25 patients with previous coronary occulsion with 3 (8.1 per cent) deaths, 48 operations were done on 41 patients with angina pectoris with an 8 6 per cent mortality.

Hannigan *et al.* (81) reported the statistics in 1951 on patients operated for cancer. There were 58 patients with electrocardiographic evidence of healed infarction. Twenty-four patients gave a history of previous coronary occlusion. Eight of these also had angina pectoris while 5 of the remaining 34 patients also gave a history of angina There were 3 (5 2 per cent)

operative deaths. The incidence of cardio-respiratory complications was greater in those who had enlarged hearts and who underwent long surgical procedures. The complication incidence was unrelated to age of infarct, angina, hypertension, sex, age or cardiac classification

De Peyster, Paul and Gilchrist (82) performed 55 operations on 33 patients with a previous myocardial infarction (7 with angina, too) with 15 (27.2 per cent) operative deaths. Lochhead *et al.* (83) reports 3 deaths in 17 patients with 30 operations (10 per cent mortality) in those patients with myocardial infarction and 2 deaths in 15 patients with angina pectoris on whom 21 operations were done (9 4 per cent mortality). Summarizing three series (81-83), Lochhead reports an operative mortality of 6 3 per cent for angina pectoris and 7.2 per cent for myocardial infarction This is based on the number of operations

Anesthetic Management: Dripps and Vandam (84) state that there is no single satisfactory approach to the anesthetic management of patients with coronary artery disease but they recommend: (1) assurance through personal contact that the anesthetist is aware of the patient's particular problem, (2) adequate sedation prior to operation, (3) smooth induction of anesthesia, (4) maintenance of blood pressure, and (5) administration of oxygen. They suggest that cyclopropane be avoided in instances where myocardial irritability is known to be increased (patients with arrhythmias), although they have anesthetized many patients with serious cardiac disease with cyclopropane and small amounts of ether. Hannigan (81) has reported a 43 per cent incidence of cardio-respiratory complications following the use of pentothal anesthesia Spinal anesthesia may result in a decrease in peripheral resistence and cardiac output and may result in coronary insufficiency However (84), despite the reduction in coronary artery flow caused by the drop in blood pressure, adequate oxygenation of the myocardium may still be present at the lower blood pressure since the heart needs less oxygen.

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Chapter VI

Congestive Heart Failure

SOMETIME in the course of the patient with coronary artery disease, congestive heart failure may ensue This need not be preceded or followed by cardiac enlargement (1). Such a patient states (2) that in recent months he has noted a decreasing capacity for exertion, and now, he has developed dyspnea at rest, orthopnea, swelling of the ankles, and other features of congestive heart failure which may include pulmonary rales, pleural effusion (58-61), hematomegaly and ascites. The cardinal points in the treatment of such a patient involve rest, diet and fluid regulation, digitalization and the administration of a diuretic (3-35). Other measures which may be of help include sedation, oxygen administration and the mechanical removal of effusions

The degree of rest and whether it be in bed or chair depends on the severity of the heart failure (3). Complete bed rest means that all activities, such as bathing and the use of a bed pan are carried out while in bed This concept may be modified by the use of a bed-side commode The object of rest is to restore compensation through the decrease in cardiac activity There has been data to show that exertion on a commode is less than a bed-pan (36) and that the patient is more comfortable when sitting up because gravity keeps the fluid in the legs instead of the lungs

The diet must regulate the salt and fluid intake (2, 3, 6, 7, 22, 26, 31, 33, 35). Some advocate the use of 1 glass of milk and 1 glass of water at intervals of an hour alternately for a total of 4 to 6 glasses of each, giving a total of 2 to 3 liters of fluid and, with the larger amount, about 1,000 calories in the form of milk, representing approximately 1.5 grams of salt (2, 5, 6). For those who cannot tolerate milk or for those who wish to feed the patients food other than milk, a diet consisting of salt-free cereals, soft and poached eggs without salt, salt-free bread, custards, junkets and such foods may be used (3). A salt-free dried or low sodium liquid milk may be given. Beer may also be used as a beverage (58) Errors in management creep in when a salt cellar is put on a low-salt diet tray or when the patient is given drugs containing sodium, such as sodium bicarbonate

The choice of a digitalis preparation is usually personal as long as one understands that all digitalis materials act through a similar mechanism and that the differences observed between one preparation and another relate to dosage, the speed of onset of effects and the duration of action (4, 5). Basically the need is for two types of digitalis preparations: one, for non-

emergent cases of congestive heart failure where digitalis may be given orally, and the other, for those who require rapid digitalization or who cannot take an oral preparation and therefore must be given digitalis intravenously.

The following is a partial list of digitalis preparations which may be given orally.

1. Digitalis Leaf Digitalizing dose is 1 to 2 gm. Maintenance dose is 0 1 to 0 2 gm Spread of digitalizing dose is 0.8 gm., followed by 0.2 to 0.4

TABLE 13

200 MG Sodium Diet

The patient must be informed that the diet is monotonous, but that by judicious use of
...lar flavoring

...upplemented
the calcium

Foods Allowed

Fruits—Fresh, frozen or unsalted canned
100 gm portions, average 0 2 mg sodium

Apple (no skin)	Peach
Apricots	Pineapple
Banana	Pineapple juice
Blackberry, fresh	Plums
Blueberry, fresh	Raspberry, black and red
Grapefruit	Strawberry
Grapefruit juice	Tangerine
Orange	Tangerine juice
Orange juice	Watermelon

Avoid all others

Vegetables—Fresh, frozen or unsalted canned
100 gm portions, average 4 mg sodium

Asparagus	Lettuce (50 gm)
Beans, green, string	Mushrooms
Beans, green, lima	Onion
Broccoli	Parsnips
Brussel sprouts	Peas, green
Cabbage	Pumpkin
Corn, sweet, yellow or white	Radishes
Cucumber	Squash
Eggplant	Tomato
Green pepper	Turnips, yellow

Avoid—Beets, beet greens, carrots, cauliflower, celery, dandelion, endive, kale, mustard greens, spinach, sauerkraut, turnips (white)

Bread—Only salt free bread, 0 5 mg sodium per 25 gm slice
or
Salt free matzoth, 0 5 mg sodium for ⅔ square

Cereal—0 5 mg sodium per serving

Oatmeal, cornmeal, Pettijohns, Maltex	2/3 cup
Instant Ralston, Wheatena, farina (not enriched)	3/4 cup
Puffed rice, puffed wheat	1 cup
Shredded wheat	1 small

(From Diet Manual, Beth Israel Hospital, New York, N Y)

TABLE 14

500 MG. SODIUM DIET

1200-2500 calories

For those physicians who do not wish to place a patient on the rigid 200 mg sodium diet, but who wish to reduce the sodium content of the diet significantly, the following diet is given

Foods Allowed

Fruits—Fresh, frozen or unsalted canned
100 gm portions, average 1 mg sodium

Apple (no skin)	Peaches
Apricots	Pears
Avocado	Persimmons
Banana	Pineapple
Blackberry, fresh	Pineapple juice
Blueberry, fresh	*Plums*
Cranberries	Prune juice
Dates	Raspberries
Grapefruit	Rhubarb
Grapefruit juice	Strawberries
Grapes	Tangerines
Grape juice	Tangerine juice
Orange	*Watermelon*
Orange juice	

Avoid all others

Vegetables—Fresh, frozen or unsalted canned
100 gm portions, average 6 mg sodium

Asparagus	Green pepper
Beans, green, string	*Lettuce (1 leaf)*
Beans, green, lima	Mushrooms
Broccoli	Okra
Brussel sprouts	Onion
Cabbage	Peas, green
Cauliflower	Pumpkin
Corn, sweet, yellow or white	Radishes
Cucumber	Squash
Eggplant	Tomato
Endive	Turnips, yellow

Avoid—Beets, beet greens, carrots, celery, dandelion, kale, mustard greens, spinach, sauerkraut, turnips (white)

Bread—Only salt free bread, 0 5 mg sodium per 25 gm slice
or
Salt free matzoth, 0 5 mg sodium per ⅔ square

Cereal—0 5 mg sodium per serving

Oatmeal, cornmeal, Pettijohns, Maltex	—2/3 cup
Instant Ralston, Wheatena, farina (not enriched)	—3/4 cup
Puffed rice, puffed wheat	—1 cup
Shredded wheat	—1 small

(From Diet Manual, Beth Israel Hospital, New York, N Y)

The following is a partial list of useful intravenous preparations of digitalis

1 LANATOSIDE C· The digitalizing dose is 1 0 to 2.0 mg. The initial dose is 1 6 mg., or when used in divided doses 0 8 mg followed by 0 4 mg every 6 hours. The onset of effects is in 30 minutes to 3 hours The excretion rate is 3 days.

2. DIGITOXIN: Dosage is same as for oral administration.

3 Ouabain: The initial dose is 0.5 mg. with 0.1 mg at 30-minute to 1-hour intervals. The digitalizing dose is 0.5 to 1.0 mg. The onset of action is 30 minutes and it disappears in 36 hours.

4 Acetyl-strophanthidin (Strophanthidin-3-acetate) (37). One mg. of acetyl-strophanthidin produces about the same intensity of effect as 0.5 mg. of ouabain. The full effect of acetyl-strophanthidin develops in a period of 10 to 15 minutes and the effect wears off in about 4 hours.

5 Thevitin (38). The digitalizing dose of thevitin is 3.78 to 7.56 mg. The

TABLE 14A

500 mg Sodium Diet

Potato or Substitute—100 gm. portions, average 1 mg. sodium
- Potato (no skin), white or sweet
- Rice, macaroni, spaghetti

Meat, Poultry, Fish or Eggs—5 oz. daily (cooked weight), average 194 mg. sodium
(1 egg daily, 1 oz. meat, poultry, or fish)

Beef	Liver	
Chicken	Veal	Only fresh water fish such as whitefish, perch, carp, pike
Lamb	Turkey	

Fats and Oils
- Sweet butter—0.25 mg. sodium per pat (6 gm.)
- Sweet cream (32%)—not more than 2 oz. daily—12 mg. sodium per oz.
- Corn oil, peanut oil, olive oil, Crisco, Spry

Beverages
- Milk—not more than 1 pint daily, 245 mg. sodium
- Tea, coffee, postum, Coca Cola

Seasonings

Allspice	Mace	Sage
Caraway	Mustard powder	Sugar, white only
Cinnamon	Nutmeg	Thyme
Curry powder	Paprika	Tumeric
Garlic	Pepper	Vanilla extract
Ginger	Peppermint extract	Vinegar
Lemon extract	Poultry seasoning	Walnut extract

Miscellaneous
- Cornstarch
- Tapioca, plain
- Unsalted nuts—almonds, Brazil nuts, chestnuts, peanuts, pecans, walnuts
- Unsalted popcorn
- Jelly, honey, jam, marmalade

Foods to Be Avoided

1 Salt, in food preparation, cooking and on table. Salt substitutes may be used *on doctor's recommendation*
2 Cheese
3 Salt water fish
4 Vegetables cooked, canned, or frozen with salt and those vegetables listed under Vegetables—Avoid
5 [illegible]
6 [illegible]
7 [illegible]
8 [illegible]
9 Baking powder

All canned, frozen packaged or bottled foods must be checked for salt or sodium content.

(From Diet Manual, Beth Israel Hospital, New York, N. Y.)

TABLE 14

500 MG SODIUM DIET

1200-2500 calories

For those physicians who do not wish to place a patient on the rigid 200 mg. sodium diet, but who wish to reduce the sodium content of the diet significantly, the following diet is given

Foods Allowed

Fruits—Fresh, frozen or unsalted canned
100 gm portions, average 1 mg sodium

Apple (no skin)	Peaches
Apricots	Pears
Avocado	Persimmons
Banana	Pineapple
Blackberry, fresh	Pineapple juice
Blueberry, fresh	Plums
Cranberries	Prune juice
Dates	Raspberries
Grapefruit	Rhubarb
Grapefruit juice	Strawberries
Grapes	Tangerines
Grape juice	Tangerine juice
Orange	Watermelon
Orange juice	

Avoid all others

Vegetables—Fresh, frozen or unsalted canned
100 gm portions, average 6 mg sodium

Asparagus	Green pepper
Beans, green, string	Lettuce (1 leaf)
Beans, green, lima	Mushrooms
Broccoli	Okra
Brussel sprouts	Onion
Cabbage	Peas, green
Cauliflower	Pumpkin
Corn, sweet, yellow or white	Radishes
Cucumber	Squash
Eggplant	Tomato
Endive	Turnips, yellow

Avoid—Beets, beet greens, carrots, celery, dandelion, kale, mustard greens, spinach, sauerkraut, turnips (white)

Bread—Only salt free bread, 0 5 mg sodium per 25 gm slice
or
Salt free matzoth, 0 5 mg sodium per ⅔ square

Cereal—0 5 mg sodium per serving

Oatmeal, cornmeal, Pettijohns, Maltex	—2/3 cup
Instant Ralston, Wheatena, farina (not enriched)	—3/4 cup
Puffed rice, puffed wheat	—1 cup
Shredded wheat	—1 small

(From Diet Manual, Beth Israel Hospital, New York, N Y.)

The following is a partial list of useful intravenous preparations of digitalis

1. LANATOSIDE C: The digitalizing dose is 1 0 to 2.0 mg The initial dose is 1 6 mg , or when used in divided doses. 0 8 mg. followed by 0.4 mg. every 6 hours. The onset of effects is in 30 minutes to 3 hours The excretion rate is 3 days.

2. DIGITOXIN: Dosage is same as for oral administration.

1. Mercuhydrin (Meralluride, U.S P.)
2. Thiomerin (Mercaptomerin)
3. Mercuzanthin (Mercurophyllin, U.S.P.)
4. Salyrgan-theophyllin (Mersalyl and theophyllin, U.S.P.)
5 Cumertilin (Mercumatilin)

Mercuhydrin (27) and Thiomerin may also be used subcutaneously

Aminophyllin, a xanthine, in doses of 0 24 and 0 48 Gm. in 10 cc of solution may also be used parenterally

The following is a partial list of the oral preparations used as diuretic agents:

1 Organic Mercurials (8, 8a, 64-66)

Neohydrin (3-chloro-mercuri-2-methoxy-propylurea)
Meralluride with ascorbic acid
Salyrgan-Theophyllin
Mercuzanthin
Mercurophyllin with ascorbic acid
Merpurate

2 Xanthines

See Chapter on treatment of angina pectoris for drugs and doses

3. Acid-forming Diuretics

Ammonium Chloride 0 5 gm.
Ammonium Nitrate 0 5 gm
Potassium Nitrate 0 5 gm

4. Diamox-250 mg Tablets

5 Urea (effervescent). 8 gm or more several times daily

6 Amino-uracil Derivatives (6, 25, 62)

Mictine (1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione) 200 mg tablets, 1 to 4 tablets daily.

7. Cation exchange resins (39-48)

The optimal routine for management of congestive failure involves a system which consists of two parts one, to abolish an attack of congestive failure, and the other, to establish an adequate plan to prevent its recurrence (7) In principle, the aim is to establish in the patient with congestive failure a state which is term and the "dry weight" By this term is meant a state in which the optimum amount of extracellular fluid remains

These are the cardinal points in the plan as outlined by Gold (7) The patient is put at bed rest, or at rest in a chair, depending on which seems preferable. The diet consists solely of 4 to 6 glasses of milk daily. The patient receives at least 2 quarts of water daily, a glassful every 2 or 3 hours If the patient has not had digitalis recently, he receives 1 2 mg of digitoxin at one time, followed by 0 1 to 0 2 mg. daily for maintenance A dose of mercuhydrin is given intramuscularly and is repeated daily The course is guided by a record of the body weight The patient is weighed before the

TABLE 14B

MEAL PLAN FOR 500 MG. SODIUM DIET

Food		1200 Calories	1500 Calories	2000 Calories	2500 Calories
Breakfast					
Citrus fruit or juice		1 serving	1 serving	2 servings	2 servings
Cereal		1 serving	1 serving	1 serving	1 serving
Bread		1 slice	1 slice	2 slices	2 slices
Butter		..	1 pat	2 pats	3 pats
Milk		6 oz.	6 oz	6 oz.	6 oz.
Sugar		..		2 teaspoons	2 teaspoons
Coffee					
Dinner					
Meat, poultry or fish		3 oz.	3 oz.	3 oz.	3 oz
Potato or substitute			1 serving	1 serving	2 servings
Vegetable		1 serving	1 serving	1 serving	1 serving
Salad		1 *serving*	1 *serving*	1 *serving*	1 *serving*
Bread		1 slice	1 slice	2 slices	2 slices
Fruit or juice		1 serving	1 serving	2 servings	3 servings
Sugar		.	..	2 teaspoons	2 teaspoons
Tea with lemon					
Supper					
Fish		2- oz	2 oz	2 oz.	2 oz
or eggs		2	2	2	2
Potato or substitute		1 serving	1 serving	1 serving	2 servings
Vegetable		1 serving	1 serving	1 serving	1 serving
Salad		1 serving	1 serving	1 serving	1 serving
Bread		1 slice	1 slice	2 slices	2 slices
Butter		.	1 pat	2 pats	4 pats
Fruit or juice		1 serving	2 servings	2 servings	3 servings
Milk		6 oz	6 oz	6 oz	6 oz
Sugar				2 teaspoons	2 teaspoons
Coffee					
Night Feeding					
Fruit or juice			.	..	2 teaspoons
Approximate Composition					
Calories		1180	1470	1975	2490
Carbohydrate	*gm*	*140*	*185*	*290*	*380*
Protein	gm	65	70	80	85
Fat	gm	40	50	55	70
Calcium	gm	7**	7**	8**	9**
Iron	mg	10**	12	14	17
Vitamin A	*I U*	*5000*	*5500*	*6000*	*6600*
Thiamine	mg	1	1.2	1.5	1.8
Riboflavin	mg	1.4**	1.5	1.7	1.8
Niacin	mg	13	14	15	18
Ascorbic Acid	mg	135	155	240	370

* For the Diabetic, replace the sugar in the diet with 1 cup of unsweetened fruit juice as a night feeding

** Below the Recommended Daily Dietary Allowances of 1948

(From Diet Manual, Beth Israel Hospital, New York, N Y)

full effect develops in a period of about 6 minutes after beginning the injection and disappears in 2 to 3 hours.

A diuretic agent is usually essential in the control of edema. Organic mercurials given by injection are the best.

The following is a partial list of parenteral organic mercurials that are used in doses of 0.5 to 2.0 cc.:

Moyer (63) reported that 500 mg per day of Diamox, given for 2 days, appeared to be about equivalent to 6 to 7 tablets (containing 60 to 70 mg. Hg) of neohydrin per day, given for the same period of time.

The cation exchange resins such as Carbo-resin, Resodec or Natrinil have the capacity to take up sodium in the intestinal tract. They have been advocated (39-48) where liberalization of the sodium content of the diet is wanted and to substitute partially or completely for a diuretic drug In practical use about one-half of the patients develop gastrointestinal symptoms. Sufficient clinical experience with the resins have resulted in a decreased use in congestive failure.

Diamox (acetazoleamide) (18, 50-52) promotes the renal excretion of base, namely sodium and potassium by inhibiting the action of carbonic anhydrase in the renal tubules. The carbonic anhydrase catalyzes the reaction of CO_2 and H_2O to yield hydrogen ions and bicarbonate If there are no hydrogen ions available for excretion into the renal tubular lumen, more sodium ions are excreted in their place or, in other words, fewer sodium ions are reabsorbed from the alkaline glomerular filtrate A 250 mg dose of Diamox will cause a 1 3-pound loss in weight in a 48-hour period (18); a 500 mg. dose of diamox will cause a 2 3-pound weight loss in 48 hours. This weight loss remains the same even if you increase the dose of Diamox to 1,000 mg. A mercurial diuretic, such as thiomerin, will give an increasing amount of weight loss in 48 hours as you increase the dose from 0 5 to 2.0 cc. It is well to remember that diamox therapy causes an increased excretion of potassium ions Agranulocytosis has also been reported (52)

"Persons suffering from congestive heart failure of moderate or severe degree frequently have had no restful sleep for many nights, and this contributes importantly to their exhaustion and anxiety In all such cases, morphine, demerol, or some other narcotic should be administered when the patient is first seen. After this sedative, preparations such as one of the barbiturates, or chloral hydrate will do " So writes Ernstene (21) who adds:

"The use of oxygen is unnecessary in the great majority of ambulant patients who have congestive heart failure When moderate or severe cyanosis is present, however, or when pulmonary edema or pleural effusion causes dyspnea with the patient well elevated in bed, oxygen often has a decidedly beneficial effect Oxygen exerts a sedative by decreasing the restlessness secondary to cerebral hypoxia. Venesection may be considered (removal of 250 cc to 500 cc of blood) whenever digitalis therapy and other measures mentioned previously fail to produce a satisfactory response and when venous pressure as noted by jugular vein engorgement is severe.

"Severe congestive failure may result in the accumulation of large amounts of fluid in one or both sides of the thorax This may further reduce the already diminished vital capacity of the lungs, and by so doing increases the

treatment is started, then every day thereafter, and the weight charted This system is continued until all gross signs of edema disappear, and the body weight reaches a resistant level below which it will not go with the continued use of the daily dose of the mercurial

The patient may now become ambulant and a plan is worked out for the purpose of maintenance In principle the following is done, the diet is increased; it is made more liberal so as to include practically all articles of food, withholding salt from the cooking and at the table Continue the 0.1 to 0 2 mg. dose of digitoxin daily. The free intake of water is also continued. The interval between the injections of the mercurial is now prolonged to every other day for 3 or 4 doses If the daily weight continues to show a constant level, the interval is increased to every third day In this way the interval is prolonged until one finds the longest interval between injections which is possible without an abrupt rise of the body weight before the injection and without a conspicuous fall after the injection. This establishes the maintenance interval and may be continued indefinitely In the course of time, it often becomes possible or necessary to make further adjustments The maintenance of the "dry" body weight is the guide There are choices of maintenance plans

What of the question of oral diuretics (10, 15, 20, 49, 23, 24, 27, 32, 29, 34) as opposed to injectable diuretics? Reports from our laboratory indicate that all the orally administered materials produce gastrointestinal distress in some patients (6) If you make the oral dose small enough you decrease the incidence of gastrointestinal symptoms but along with this goes the diuretic response The range of utility of oral diuretics is limited None are free of unpleasant gastrointestinal side-reactions It is not possible with any of the orally administered material to secure such diuretic effects as follow the intramuscular injection of mercuhydrin or similar injectable mercurials in doses of the order of 2 cc. without a prohibitive incidence of gastrointestinal distress The average diuretic responses to most of the orally administered materials are in the range that would be represented by about 0 5 cc. of mercuhydrin by the intramuscular route. Neohydrin in doses of 3 to 6 tablets daily, will produce a diuretic response equal to 1 cc of injection mercuhydrin (8) A daily dose of 6 to 8 gm of ammonium chloride causes a diuretic effect which is equivalent to approximately that of 0 5 to 0 75 cc. of mercuhydrin given intramuscularly (8). To get this effect, in about half of the patients gastrointestinal side effects will occur When the patient has been given 6 to 8 gm of ammonium chloride before mercuhydrin, it will enhance the effect of 1 cc. of mercuhydrin so that it has the diuretic effect similar to 2 cc. of mercuhydrin injected without ammonium chloride. One gm of Mictine (62) has been shown to have an effect equal to about 0 8 cc. of intramuscular mercuhydrin

The low salt syndrome involves reduction in values of serum sodium, chloride and carbon dioxide The normal values of approximately 140 mEq. of sodium, 100 mEq of chloride and 25 mEq of carbon dioxide (50 to 60 volumes per cent) may be lowered to levels such as 125 mEq, 85 mEq, and 14 mEq. (30 volumes per cent), respectively (14) According to Blumgart (14), this syndrome may be due to repeated injections of mercurial diuretics, particularly if salt intake has been restricted, the cation exchange resins have been employed, or perspiration has been excessive. The amount of salt administered in this manner should be calculated from the serum values after determining the magnitude of the existing deficit He states (14) that the low sodium syndrome (hyponatremic acidosis) occurs because of low sodium diets and vigorous mercurial diuretic therapy The clinical symptoms and signs of the low salt syndrome (weakness, drowsiness, headache, thirst, nausea), the low urinary volume, the refractoriness to diuretics, and the presence of renal disease suggest the presence of the low sodium syndrome The diagnosis is confirmed by finding a decrease in the serum sodium from the normal value of approximately 140 mEq. to 125 mEq or less per liter. The blood carbon dioxide combining power is generally below 30 volumes per cent Treatment consists in the intravenous administration of sodium bicarbonate, one sixth molar sodium lactate solution, or, at times, sodium chloride, to repair the chloride as well as the sodium deficiency.

Rubin *et al* (53) have indicated that in patients with refractory edema and normal electrolytes, responsiveness to mercurials can be invoked again by Diamox or a combination of Diamox and ammonium chloride The mechanism is the production of a hyperchloremic acidosis followed by mercuhydrin When Diamox and mercuhydrin are administered on the same day, optimal diuresis does not occur Maximal diuresis with mercuhydrin occurred the second day after Diamox was discontinued The regimen is as follows. 750 mg. of Diamox daily for 3 days together with 10 gm of ammonium chloride After the third day, the Diamox is discontinued, the patient is kept on ammonium chloride, and on the fifth morning, the mercurial is given

The presence of hypopotassium is diagnosed by finding the plasma potassium concentration reduced below the normal of 4 to 5 mEq per liter or observing characteristic electrocardiographic alterations. The effectiveness of the mercurial diuretics may be improved by the administration of 2 to 3 gm of potassium chloride or potassium citrate four times daily (14)

Another method of treating refractory heart failure when all else fails involves the lowering of the metabolic rate and hence the bodily requirements for blood by chemical thyroidectomy which involves the use of one thioureas or radioactive iodine (55, 56) This is covered under medical therapy for angina pectoris (Chapter IV).

degree of dyspnea. Whenever extensive pleural effusion is present, therefore, the fluid should be removed as completely as possible by prompt thoracentesis.

"Although ascites is a not infrequent complication of advanced decompensation, the amount of fluid is usually not sufficient to embarrass respiration seriously or add importantly to the patient's distress."

Refractory Heart Failure (53, 2, 14, 21, 54): What do you do with the patient who has been on the maintenance regime and then becomes refractory to the treatment? That is, he seems to go into further heart failure The first question to be asked is are all points of our maintenance regime being followed correctly (14)? For example, has the patient been completely digitalized, that is, has this digitalization been adequate on rest and inadequate because the patient is now exerting more effort? On the other hand, does the patient need more rest than has been provided? Does he need more sedation to provide more restful nights? Is his bed or his position in bed uncomfortable? Have we restricted the sodium intake sufficiently? Is salt creeping into the diet through errors of commission or omission? Has the patient gotten complete benefit from the use of diuretics? Has the injection been made into edematous areas where absorption is unsatisfactory? Does he need a potentiating diuretic, such as ammonium chloride or aminophylline a day before the diuretic is given?

Is there another etiologic condition which may have sent the patient in further heart failure, such as a painless acute myocardial infarction, a pulmonary embolism or infarction, an intercurrent infection, hypoprotinemia, anemia, a cardiac arrhythmia or thyrotoxicosis. In general we look for conditions which might impose additional work on the heart or might weaken the heart. There is of course a group in which heart disease has progressed to a point where cardiac output has fallen so far as to be inadequate to maintain sufficient renal function This is the terminal phase in the natural history of heart disease.

In the course of the management of congestive heart failure, certain imbalances may occur in the electrolytes, that is sodium alone, chloride alone, both together, or in the potassium balance.

In the majority of patients with heart failure who develop diuresis from any cause, the amount of chloride which appears in the urine is high in relation to the sodium loss This produces slight or moderate decreases in chloride and a hypochloremic alkalosis which is usually of moderate degree and inconsequential but may be exaggerated in patients who lose huge volumes of fluid, usually in association with the use of mercurial. The use of ammonium chloride in doses of 4 to 6 gm. by mouth during the period of the most marked diuresis in the treatment of congestive failure can be used to replace chloride.

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Ligation of the inferior vena cava (57) has also been suggested in the treatment of refractory heart failure but has more usefulness in rheumatic heart disease than in coronary artery disease (57a).

Acute left ventricular failure is characterized by the sudden onset of dyspnea, orthopnea, cough and frothy sputum. Cyanosis, cold sweat and great anxiety may be seen. The patient usually has to sit up straight in bed and coarse rales are heard over the lung fields The following measures may be used in treatment.

Oxygen (by tent or mask) (a positive pressure mask may be used),

Ten to 15 mg. of morphine sulfate except where chronic pulmonary disease is suspected;

Aminophylline in a dose of 0 24 or 0.48 gm in 10 cc intramuscularly or intravenously;

A rapidly acting digitalis glycoside provided that there is no question of digitalis ingestion in the preceding two weeks and a mercurial injection intramuscularly.

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daily is sufficient. In more stubborn cases, as much as 0 6 gm. every three hours, or about 4 gm daily proves to be necessary. Electrocardiograms should be taken before and after each new dosage to study effects on width of the QRS. The prolongation of the QRS time begins at about levels of 3 gm. daily If the QRS time increases to 0.12 second or more, quinidine should be discontinued It is also wise to study the rate and the electrocardiogram before the succeeding dose because a rate of 130 beats per minute may be due to sinus rhythm plus vagal blocking by quinidine.

The following preparations of quinidine are available.

1. Quinidine Sulfate in capsules or tablets 0 2 or 0.3 gm. or a 5 per cent suspension in syrup 0 2 gm. per teaspoon

2 Quinidine lactate (0 65 gm in 10 cc) for intravenous and intramuscular use (4).

3 Quinidine Sulfate in propylene glycol (20 per cent) (0.2 gm in 1 cc) for intramuscular use (5).

Quinidine may cause impairment of hearing, ringing in the ears, blurred vision, lightheadedness, giddiness, tremor, nausea, vomiting, abdominal cramps and rarely convulsion Idiosyncracies include fever, urticaria, asthma, and purpura (3, 6, 7) The toxic actions on the heart include prolongation of A-V conduction, intraventricular block, premature contractions, ventricular tachycardia or fibrillation (7, 8).

The principle of treatment involves the knowledge that accumulation comes to an end in a period of 4 or 5 days If treatment is begun with a dose of 0 3 gm , taken at intervals of 6 hours for 3 doses daily, and the abnormal rhythm (premature beat) is still present after the first day, the same dose should be continued for 4 or 5 days, for during that period the intensity of action will increase If at the end of this time, the therapeutic end has not been achieved, the daily dose is raised and tested for 4 or 5 days. This is done until the rhythm is brought under control providing no toxicity results

Pronestyl (9): Pronestyl hydrochloride capsules are available in doses of 0 25 gm and in 10 cc. vials containing 100 mg per cc. It is best used for ventricular arrhythmias although it has also been given for the auricular ones too In general, a 4 gm dose of pronestyl will do about the same thing that is to be expected from 1 gm of quinidine The general pattern of its action is similar to that of quinidine, both with respect to the kind of cases, the results and the toxic effects (10)

Digitalis: Digitalis preparations may be used to control such abnormal rhythms as auricular fibrillation, paroxysmal auricular tachycardia, A-V nodal rhythm and auricular flutter The available preparations have been considered in the section on Congestive Heart Failure.

Chapter VII

Disorders of the Heart Beat in Coronary Artery Disease

Any of the types of ectopic rhythms, some grave and some of lesser moment, may present themselves during the course of coronary artery disease The most common are auricular and ventricular extrasystoles and auricular fibrillation (1).

According to Bellet (1) an ectopic rhythm may be suspected from the following (and confirmed by the electrocardiogram)

1 History of sudden onset of rapid rate
2. Any irregularity of cardiac rhythm.
3 A regular rhythm when the rate is below 30 or above 140 per minute.
4. Coincidence of rapid rate with onset of failure.
5 Sudden halving of rate following carotid sinus pressure
6. Variation of intensity of first heart sound with rapid rate.
7. No change in rate from moment to moment after exercise

DRUG THERAPY IN DISORDERS OF THE HEART BEAT

The three major drugs which are used in the treatment of disorders of the heart beat are digitalis, quinidine and pronestyl.

Quinidine: Gold (2) has found quinidine to be effective in the treatment of the following disorders of cardiac rhythm.

1. Premature contractions or extrasystoles (auricular, nodal, ventricular).
2 Paroxysmal auricular tachycardia.
3. Nodal tachycardia.
4. Auricular flutter
5 Auricular fibrillation.
6 Ventricular tachycardia.
7 Ventricular fibrillation.

In patients with paroxysmal disorder of rhythm in whom the presenting problem is to prevent attacks, Gold (2, 3) begins with a daily dose of 1 gm in the form of 0.3 gm (5 gr.) three times daily. If and when an attack occurs, the daily dose is increased by 0 3 gm. (5 gr.). This is usually accomplished by first shortening the interval between doses, and then increasing the size of the daily dosage after each attack is continued until a level is reached at which paroxysms no longer occur. The required daily dosage varies greatly In some the initial dosage of 0 3 gm. three times

continued the same doses for 24 to 48 hours, when the schedule was changed to 6-hour intervals, and later further reduced The average maintenance on the 6-hour schedule was one-half that necesary for reversion. When on the 4-hour schedule the 4 A M dose may be omitted if it is added to the midnight dose in the enteric coated form, which has its peak of absorption 5 to 6 hours after ingestion. It is recommended that anticoagulants be used for several days before and for at least two weeks after the use of quinidine to prevent possible emboli during the conversion

Auricular Flutter (14-20a): Digitalis is a drug of choice in the treatment of auricular flutter (Fig 35C). The course of events is in most instances for the flutter to change to fibrillation and then revert to normal sinus rhythm Quinidine and pronestyl may also be used The dose is as indicated for auricular fibrillation Hoffman and Pomerance (20a) have indicated that 90 per cent of the causes of auricular flutter are associated with organic heart disease, with about 40 per cent due to hypertensive-arteriosclerotic heart disease The characteristic findings in the electrocardiogram are. (1) absolute regularity of the auricular (F) waves; (2) demonstration in any one lead that the iso-electric period does not exceed 0 04 second, (3) atrial rate of 200 to 360 with the ventricular rate a fraction of the atrial.

Ventricular Tachycardia (21-25) (Fig 36C) Quinidine and pronestyl are the drugs of choice and are effective in from one-half to two-thirds of the cases. They have been given orally and intravenously. Quinidine orally is given in doses of 0 4 or 0 6 gm every 2 or 3 hours Because of the hazard of cardiac standstill in the abrupt termination of the rapid ectopic rhythm, the aim should be to slow the tachycardia to a rate which may be permitted to continue for some time without impairing the circulation, for example, from an initial rate of 200 per minute to 120 or 110 per minute Gold (2) states that when the heart functions under these circumstances for some time at the slower rates, the other pacemakers recover and become ready to take over promptly when the ectopic rhythm is abolished without the delay which may give rise to a convulsion, when a rapid rhythm is brought to an end abruptly It is always wise to take electrocardiograms before each successive dose is given to determine whether auricular activity is present.

The pronestyl may be used orally, intramuscularly or intravenously The oral dose is 0.5 to 1 0 gm given every 2 to 4 hours Where a more rapid effect is desired, a parenteral administration of 0 5 to 1 0 gm. at a single dose may be used. The intramuscular route is safer The maintenance dose following conversion is 250 to 500 mg. four times daily.

Magnesium sulfate in doses of 15 to 20 cc of a 20 per cent solution has been used Potassium Chloride, 2 gm. orally, every 2 to 4 hours, has also been suggested (1) where digitalis is the cause of ventricular tachycardia.

Ventricular Fibrillation: Ventricular fibrillation (26) represents an emergency of the highest order and requires action within minutes involving

b. QUINIDINE. Quinidine may be used during an attack of paroxysmal auricular tachycardia and as a preventive measure between attacks. The method of administration in dose has been discussed.

c DIGITALIS: Intravenous digitalis is useful in stopping the attack while maintenance doses may prevent the recurrence. Bellet (1) recommends Lanatoside C (Cedilanid) (0 8 mg.) intravenously or Digalen (2 to 4 U.S.P. units) La Due (12) found it more successful to give a single dose of 1 6 mg of Lanatoside C intravenously at one time in a period of 3 to 5 minutes. Transient nausea and vomiting occurs in about 8 per cent of patients given the drug in this dose.

d PRONESTYL: The oral doses range from 250 mg. to 500 mg. four times a day The intramuscular dose ranges from 250 mg. to 500 mg and may be repeated in two or three hours or sooner if the attack is not terminated.

e. OTHER DRUGS. The following drugs have proved useful in the treatment of paroxysmal auricular tachycardia, but should be used with all caution in the presence of coronary artery disease.

1 Neostigmine (prostigmine) may be given subcutaneously or intravenously in doses of 1 0 to 2 cc of a 1.2000 solution The maximum effect occurs in about 20 minutes (13).

2. Acetyl-B-Methyl Choline (Mecholyl) is given subcutaneously in a dose ranging from 2 5 to 60 mg, in an average dose of 25 mg. Effects occur in 1 or 2 minutes

3. Magnesium Sulphate: The usual intravenous dose consists of 10 cc. *of a 10 per cent solution*

Auricular Fibrillation: The treatment of auricular fibrillation (Fig. 35D) whether paroxysmal or chronic, is best accomplished by digitalization. Paroxysmal auricular fibrillation may also be treated by quinidine or pronestyl. It is not the usual procedure to attempt to convert the chronic auricular fibrillation of patients with coronary artery disease to normal sinus rhythm. Many believe that maintenance of such a patient with a heart rate of 70 to 80 beats per minute provides adequate cardiac function. However, there are those who feel that conversion to normal sinus rhythm should be attempted in those with auricular fibrillation of short duration in terms of months, in those who have sustained embolic phenomena, and even in those with chronic auricular fibrillation to better the cardiac function and to prevent possible future emboli.

The conversion is accomplished by the use of quinidine (21). Yount *et al.* (14) recommend the following dose schedule: quinidine 0.2 gm every 4 hours day and night, increasing by 0.1 gm. per dose at the end of each 24 or 48-hour period. In their series, reversion occurred on the average after 6 days on a mean dose of 0.42 gm. every 4 hours. The duration and the severity of the disease did not influence the result. The oldest patients responded most readily and on the smallest doses. After reversion they

Isopropylarterenol (Isuprel) hydrochloride is administered in doses of 10 to 15 mg. sublingually or 0.02 mg. intravenously (31).

The external electric stimulator, as devised by Zoll (33, 36) may serve as the cardiac pacemaker in certain instances of ventricular standstill (33, 34). A negative electrode is placed at the cardiac apex and a positive electrode on the right anterior chest. An electric stimulus is automatically provided to the dormant heart which responds with a ventricular contraction.

Chandler and Rosenbaum (35) used both a cardiac pacemaker and

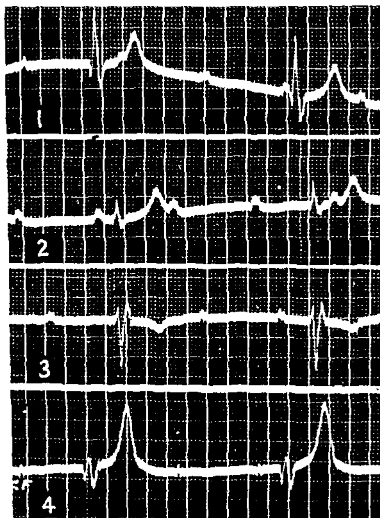


Fig 37 Electrocardiogram showing complete heart block of a 53-year-old male with arteriosclerotic heart disease Auricular rate is 75 beats per minute, ventricular rate, 30 The patient had Adams-Stokes' seizures due to asystole which were controlled by ephedrine sulfate, 24 mg, given orally four times daily

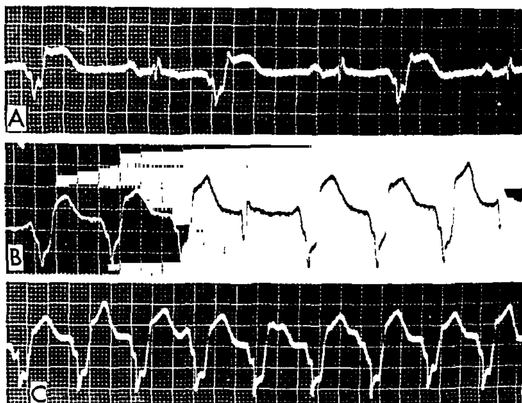


Fig 36 Electrocardiogram of a 70-year-old white male with arteriosclerotic heart disease showing Lead II with· (A) spontaneous ventricular premature beats in coupled rhythm, (B) three ventricular premature beats for each normal beat, and (C) ventricular tachycardia (Courtesy of Dr Louis Friedfeld)

thoracotomy and cardiac massage The drug of choice is pronestyl intravenously

Heart Block with Adams-Stokes' Attacks: The stoppage of cardiac output during asystole or cardiac arrest may occur in complete heart block (Fig 37) and result in syncope or a convulsion referred to as an Adams-Stokes' attack (27-34). Isuprel is the drug of choice (28-32) when the mechanism for the Adams-Stokes' attack is ventricular tachycardia or fibrillation, and when ventricular asystole alternates with tachycardia or fibrillation. Epinephrine, ephedrine or paredrine are the better drugs for ventricular asystole unaccompanied by ventricular tachycardia or fibrillation Pronestyl should *not* be used in the treatment of ventricular tachycardia in the presence of complete heart block and Adams-Stokes' seizures

Epinephrine is given subcutaneously in doses of 0 4 to 1 0 mg , ephedrine sulfate orally in doses of 15 to 30 mg , three to five times daily, and paredrine, 20 to 60 mg., three times daily Barium chloride may also be tried (15 to 60 mg , three to four times daily) Corticotropin (ACTH) has been suggested in doses of 40 mg by Prinzmetal (20).

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Isuprel in treating a severe Adams-Stokes syndrome. Isuprel was given sublingually (20 mg.), subcutaneously (0.2 mg.), intravenously (1 mg in 200 cc. of 5 per cent glucose), and intramuscularly (1 mg.) at varying times.

Bellet, Wasserman and Brody (37) have used molar sodium lactate to increase the rhythmicity of the cardiac pacemaker. In 3 of 4 patients with Stokes-Adams' disease, molar lactate restored ventricular beating on numerous occasions. The dose in 1 patient was 80 cc. intravenously by syringe in a period of several minutes. In another case, repeated injections of 40 to 60 cc. consistently restored ventricular beating in each of multiple episodes.

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Chapter VIII

Acute Myocardial Infarction

THE CLINICAL features of angina pectoris were well established in 1768, but it was not until 1912 (1) that James Herrick brought to the lasting attention of the world the clinical features of coronary occlusion, even though others (2, 3, 4) had previously published accounts of this disease, beginning with the year 1878

In at least 95 per cent of the patients with acute coronary occlusion, arteriosclerosis of the coronary arteries is the underlying cause. According to Horn and Finkelstein (5), coronary artery closure was found to be due to intramural hemorrhage in 62.5 per cent of their 100 cases of acute arteriosclerotic coronary artery occlusion and to formation of a thrombus on an arteriosclerotic plaque in 37 5 per cent of the cases. Myocardial infarction need not, however, always accompany coronary occlusion because a slow occlusion in the presence of adequate collateral circulation may not cause myocardial ischemia and resultant infarction On the other hand, as a result of pulmonary embolism, severe acute anemia or following operative procedures, a myocardial infarction may occur without coronary occlusion.

Ernstene (6) reports that in general, sudden occlusion of the anterior descending branch results in infarction in the anterior apical portion of the left ventricle with or without involvement of the interventricular septum, while occlusion of the circumflex branch causes infarction in the posterolateral or posterior basal portion of the left ventricular wall Sudden obstruction of the right coronary artery is followed by infarction of the posterior basal portion of the left ventricle. Coronary occlusion occurs with almost equal frequency in the left anterior descending and the right circumflex arteries, while occlusion of the left circumflex occurs less often

Clinical Features: The interruption of the blood supply of the coronary artery leads to infarction of the myocardium and a clinical picture which may include severe pain, fever, variation in the level of the blood pressure, pericardial friction rub, gallop rhythm, elevation of the sedimentation rate, leucocytosis and changes in the electrocardiogram

Pain is the commonest and most prominent symptom of the attack. The *location of the pain is most often substernal but may be located* also in the epigastrium, precordium, left shoulder and back Epigastric pain is a variant of substernal pain The pain usually lasts 24 hours and then subsides. Preinfarction angina may occur and probably represents sudden narrowing of the lumen of the coronary artery by sub-intimal hemorrhage and the prolonged severe pain, the final thrombosis and complete occlusion (7-11).

Feil (7) estimates that premonitory symptoms are present in approximately 50 per cent of all patients, and Master, Dack and Jaffe (9) reported an incidence of 44 per cent in 260 cases.

Myocardial infarcts, both old and recent, have been found at post-mortem examination in patients in whom there was no history of chest pain or of a clinical episode suggestive of coronary occlusion The occurrence of painless infarction has not been correlated with either the location (12), size (13) or age of infarct (14), nor with the age of the patient (15)

Explanations for painless infarcts are variable. Herrick (16) has stated that "it has been suggested that normally certain areas of the heart are not only less vital than others, indifferent or silent they have been called, but also less sensitive At autopsy fresh infarcts are sometimes found associated with multiple areas of fibrosis that speak for previous obstruction of small branches, yet no pain has been noted, no pain even announcing the recent infarction. There has evidently been a very gradual and progressive narrowing of the artery by sclerotic processes The area irrigated by the artery has become relatively inactive, relatively anesthetized by destruction of vessels, nerves and functioning muscles, so that a painful response to the new obstruction comes without a sudden shock, the element of surprise is lacking. The final complete obstruction comes without a sudden shock, the element of surprise is lacking as the heart is in a sense prepared for the supreme insult. Abrupt heart failure with its dyspnea and other phenomena may be present, but pain is lacking."

Reported instances of the occurrence of painless myocardial infarction are fairly numerous in the literature Some of these reports deal with individual case histories (19-22) Other authors have analyzed the incidence of painless infarctions in larger series of myocardial infarctions (see Table 15) and the estimates vary from 1 per cent to 61 per cent This variation in incidence seems to depend on several factors (1) Was the taking of an adequate history rendered difficult by such factors as sudden death, coma, surgical anesthesia, presence of psychosis (22a), and cerebrovascular accident? (2) Were mild painful episodes regarded as angina pectoris, rather than the mild pain of myocardial infarction, and were such equally characteristic sensations of myocardial infarction as pressure, constriction and burning distinguished from pain? (3) Were such complicating conditions as congestive heart failure or debilitating disease present to explain the absence of pain? Notwithstanding, there is sufficient agreement among these authors so that one can definitely state that painless myocardial infarction may be said to occur under the same standard conditions as painful infarction

It is well to remember, as Davis (24) has pointed out, that "coronary thrombosis with a syndrome characterized by the abrupt onset of dyspnea and heart failure, unprovoked by effort, may be more common than is gen-

TABLE 15

INCIDENCE OF PAINLESS MYOCARDIAL INFARCTION

Author and Reference	*No of Cases in Series*	*No Painless Infarctions*	*Per Cent Painless Infarctions*	*Remarks*
Levine & Brown 1929 (23)	46	22	48	All had post-mortem confirmation
Davis 1932 (24)	76	29	38	53 of 76 patients had pathological confirmation
Saphir 1935 (25)	34	13	38	All had post-mortem confirmation
Bruenn 1936 (26)	31	19	61	All had post-mortem confirmation
Boyd 1937 (27)	127	42	33	Clinical
Kennedy 1937 (28)	200	8	4	All autopsy cases 109 had old infarcts 142 had recent infarcts 51 old and recent infarcts
Gorham & Martin 1938 (29)	100	42	42	All had post-mortem confirmation
Master 1938 (30)	35	21	60	All post-operative coronary occlusion
Gross & Engelberg 1940 (31)	100	25	25	All had post-mortem confirmation
Pollard & Harvill 1940 (32)	375	25	8 5	Clinical and autopsy cases
Yater 1948 (33)	400	4	1	Survivors of myocardial infarcts
	242	6	2 5	Autopsy cases
Mintz & Katz 1948 (34)	382	18	3 4	Clinical and autopsy cases
Landman 1949 (35)	255	28	11	All had post-mortem confirmation
Babey 1939 (36)	116	1	0 8	Clinical and necropsy
Stroud & Wagner 1941 (37)	49	13	26	Clinical and necropsy
Levine & Rosenbaum 1941 (38)	208	6	2 8	Clinical and necropsy
Kugel 1945 (39)	350	10	2 8	Clinical
Billings *et al* 1949 (40)	205	20	9 7	Clinical and necropsy

erally believed, that this syndrome may be due to the formation of an area of absolute ischemia, and anemic infarct whereas the syndrome characterized by severe, enduring, substernal or epigastric pain unprovoked by effort is due to the formation of an area of relative ischemia "

Besides pain, other symptoms are found in acute myocardial infarction. Dyspnea may represent acute pulmonary edema or pulmonary congestion due to acute left ventricular failure. It is not unusual to find some transient rales at the base of either lung (24a) during the first hours after the acute infarction. These rales clear spontaneously and do not represent an indication for digitalization. Dyspnea, as indicated above, is the most common symptom in painless myocardial infarction.

Such vasomotor symptoms as blanching, cold sweats, pallor are found initially especially in the presence of shock. The co-existence of a cerebrovascular accident with coronary thrombosis (41) must be considered as a neurologic manifestation. If syncope or convulsions occur, beside the actual coronary occlusion, one must consider an Adams-Stokes' attack, a paroxysmal arrhythmia or a calcific aortic stenosis Gastrointestinal symptoms include nausea, vomiting and diarrhea

Laboratory Tests in Acute Myocardial Infarction: The standard tests during acute myocardial infarction may reveal leucocytosis, an elevated sedimentation rate, hyperglycemia, and an abnormal electrocardiogram. As an indicator of myocardial necrosis, the sera of such patients may also reveal abnormalities in the C-reactive protein (42, 43), the glutamic oxalacetic transaminase (44-46) and the fibrinogen (47). The C-reactive protein correlates roughly with the degree and persistence of fever, leucocytosis and the elevated sedimentation rate (43) The test is negative in patients with typical coronary insufficiency but without the criteria for myocardial infarction (42).

The serum glutamic oxalacetic transaminase enzyme is present in the normal human in a range of 10 to 40 units (44a) The more severe the myocardial necrosis, the higher the level of serum transaminase It is highest during the first 24 hours after coronary occlusion Steinberg and Ostrow (46) report that the transaminase level after transmural myocardial infarction was elevated in the range of from 65 to 308 units per ml, with a mean peak of 168 units per ml These peak values were reached within 36 hours after onset of infarction, and fell to normal on the average by the sixth day Knowledge of the absolute level of the serum transaminase or of serial levels would be especially useful in the following clinical situations associated with myocardial infarction Where a left bundle branch block exists and the electrocardiographic changes associated with acute anterior wall infarction may be hidden (200), where status anginosus exists either with no elec-

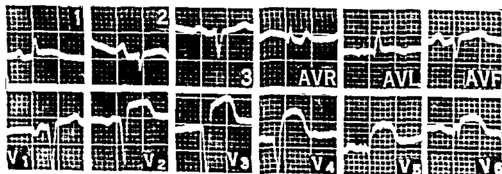


Fig 38 Acute anterior wall infarction in a 60-year-old white male.

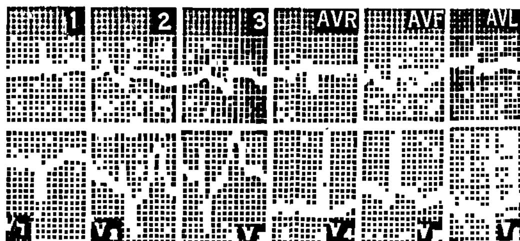


Fig 39 Acute posterior wall infarction in a 52 year-old white male

trocardiographic changes or with those indicative of coronary insufficiency (S-T segment depression and or T wave inversion) (44a), and where chest pain recurs during the course of acute myocardial infarction and the clinical possibility of an extension of the original infarction exists.

Electrocardiographic Patterns of Acute Myocardial Infarction: The changes in the electrocardiogram which are characteristic of acute myocardial infarction involve the anterior and posterior surfaces of the heart most commonly but not infrequently they appear in combination with involvement of the septal or lateral areas. Elevation of the S-T segment and inversions of the T wave with the subsequent appearance of a Q wave occurs predominantly in lead 1 and aV1 in anterior wall infarction (Fig. 38) or lead 3 and Vf in posterior wall infarction (Fig. 39), with reciprocal depression of the S-T segment in lead 3 or lead 1, respectively The T wave at first may be high (48) but subsequently it becomes depressed and inverted to a V shape. The typical changes may last a few hours or a few days and the electrocardiogram may subsequently return to normal or the abnormal Q wave may persist for a life time Combined anterior and posterior wall infarctions (Fig 40) may occur (48a). Electrocardiographic changes may be absent in this combination when the altered electrical forces neutralize each other In most instances, the recent evidences of infarction are superimposed on the old

Anterolateral changes (49) involve the R-ST segment and T wave of leads V_4, V_5 and V_6. Anteroseptal infarcts show changes in V_1 and V_2 or one or more of V_2, V_3 or V_4. Posterolateral infarction involves V_5 and V_6 with the R and T waves in V_1 and V_2 prominent.

A course of acute myocardial infarction may present fever, mild leucocytosis, elevation in the sedimentation rate and progressive changes in the T wave of lead 1 and perhaps leads V_5 and V_6 only. These changes may

develop slowly. Where a history of chest pain is typical, one should wait 2 weeks for some electrocardiographic changes before writing off the possibility of myocardial infarction. The changes in T waves only points out a diminution of blood supply to the anterior wall but not sufficient to cause discrete areas of necrosis or injury. On occasion, isolated deeply inverted T waves in the precordial electrocardiogram may be indicative of myocardial infarction (50, 51).

Lateral apical wall infarctions present abnormalities in V_5, V_6 and V_1. Lateral left ventricular infarction presents R-ST depression in lead I and II, and IV and no abnormalities in lead III (52, 53) High anterior lateral myocardial infarction may show an abnormal Q wave in V1 only (54-56). Unipolar precordial leads should be taken in higher intercostal spaces at the location of V_3, V_4 and V_5. Such leads usually show an increase in the depth of the Q wave, a decrease in the height of the R wave and the presence of a diphasic or inverted T wave, all indicative of myocardial damage (Figs. 41 and 42).

In the presence of right bundle branch block, the signs of anterior infarction do not usually appear in the limb leads The precordial leads, however,

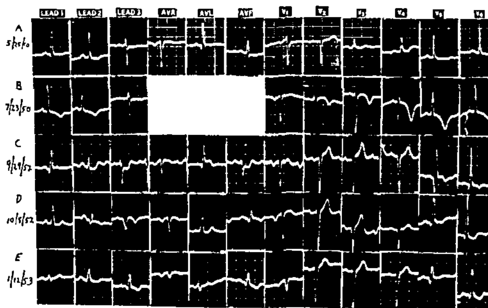


Fig 40. Electrocardiograms of a 55-year-old white female with arteriosclerotic and hypertensive heart disease demonstrating combined anterior and posterior wall infarction Tracing A, taken on May 25, 1950, shows myocardial damage. Tracing B was taken during the course of an acute anterior wall infarction; tracings C and D during an acute posterior wall infarction Tracing E was taken about 3 months after the posterior infarction and shows predominantly the electrocardiographic residue of the posterior wall infarction.

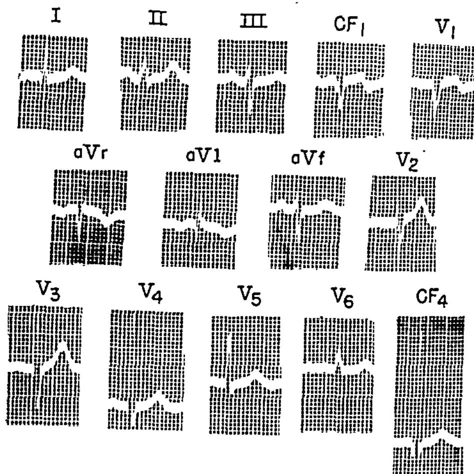


Fig 41 Diagnosis. arteriosclerosis, enlarged heart, dilated aorta, regular sinus rhythm, IIIc. Electrocardiogram showing normal standard and unipolar extremity and precordial leads except for aVl which shows a significant Q wave

will show alterations in the QS deflections and Q waves as is usual in infarction. Changes are most often confined to the right side of the precordium (49) Posterior wall infarction exhibits signs in leads Vf, II and III

In the presence of left bundle branch block, the electrocardiographic presence of acute myocardial infarction is very difficult to discover Diagnostic changes in the QRS and RS-T waves fail to appear Either one has to rely on the clinical picture or look for some serial alterations of the electrocardiogram during the course of the illness. This likewise applies in the presence of the Wolff-Parkinson-White Syndrome (57, 58) Kennamer and Prinzmetal (197) suggest that, in patients with left bundle branch block for whom a preinfarction tracing is available for comparison, the following changes are diagnostic of acute myocardial infarction: decrease in the magnitude of the R wave or elevation of the S-T segment in the precordial leads overlying the left ventricle or aVf.

The diagnosis of atrial infarction (59-62), electrocardiographically, involves changes, either elevation or depression, of the PR segment and the sudden development of atrial arrhythmias. The PTa segment (61), the terminal portion of the PR segment that is representative of the period of atrial repolarization, is elevated in lead 1, aVl and the anterior precordial leads in anterior atrial infarction and in leads 2, 3 and aVf in posterior atrial infarction.

It is interesting to note that Gittler, Schack and Vesell (198), after reviewing the 1-year electrocardiograms of 51 patients with acute myocardial infarction, found that in only 1 of the 51 instances did the 12-lead electrocardiogram with typical changes return to normal 1 year later. They concluded that a completely normal 12-lead electrocardiogram is strong evidence against the presence of an acute myocardial infarction of the classical anterior or posterior wall type, 1 year previously.

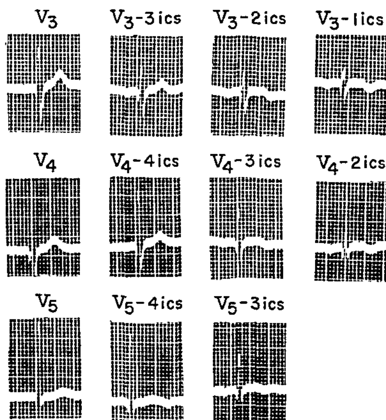


Fig 42. Electrocardiogram on same patient as Figure 41. Unipolar precordial electrocardiogram taken at the usual location of V_3, V_4 and V_5 and at intercostal spaces above this Note the increase of the depth in the height of the R wave, and the change in the direction of the T wave in V_3 This is taken as evidence of myocardial damage.

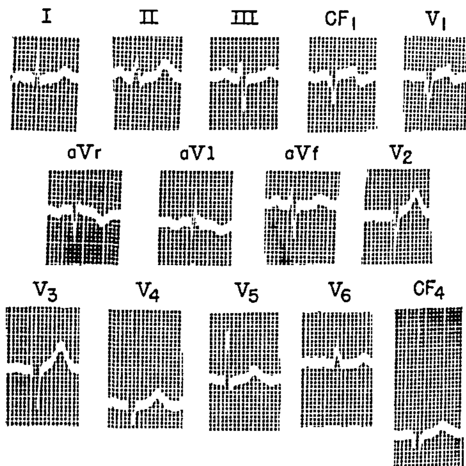


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diogram with a dose of nicotine or tobacco smoke one-fourth as large as that which causes slight changes in the dog with normal coronary arteries. It is of interest to note that this increased response to nicotine diminishes as healing takes place.

Long-term therapy after an acute myocardial infarction has been directed in recent years at the atherosclerotic process itself. For example, attempts have been made to lower the level of the serum cholesterol or the serum lipoproteins by the low fat-low cholesterol diet, by sitosterol administration, by heparin administration and by the use of estrogens. Long term anticoagulant therapy with dicumarol has been suggested to prevent future thrombosis or embolism.

ANTICOAGULANTS: The use of anticoagulants in coronary heart disease has been suggested for three phases by Nichol, Phillips, and Jenkins (67): (1) impending myocardial infarction and acute coronary insufficiency, (2) acute transmural myocardial infarctions, and (3) following recovery from either of the foregoing situations, for long term prevention of recurrent attacks.

There are two main types of anticoagulants which are in clinical use (68, 69). (1) the prothrombin depressants including the coumarins like Dicumarol, Tromexan, Cumopyran, Marcoumar and Coumadin sodium (Warfarin), and indandiones like phenylindandione, and (2) the sulfonated polysaccharides like heparin.

HEPARIN. Nichol (67) uses the following method of heparinization. The initial dose is 50 mg given intravenously after dilution to 5 cc. normal saline. Before the actual injection of heparin, at the same venipuncture, blood is drawn for a controlled Lee-White coagulation time and prothrombin time. In addition, 50 mg of concentrated aqueous heparin is given deep in the subcutaneous tissues of the buttock or thigh Four hours later a coagulation time is obtained as a rough index of the patient's sensitivity to heparin, and, if under 30 minutes, 50 mg of concentrated heparin is given every four hours for three doses. The coagulation time is again determined and if found under 30 minutes the same four hour schedule is continued for 4 doses If the coagulation time is 30 to 60 minutes, the interval of heparin injection may be increased from 5 to 6 hours If it is excessively high, no heparin is given and the test is repeated in 6 hours at which time the heparin dosage is regulated anew The maintenance dosage is about 50 mg. every 5 to 6 hours for that dosage which keeps the level at three times the usual clotting time It is most usual to begin dicumarol alone with the first dose of heparin By the third day, dicumarol should be actively exerting an anticoagulant effect The effects of heparin are counteracted by protamine, mg for mg

Engelberg (70) reports subcutaneous administration of daily doses of

Treatment of Acute Myocardial Infarction: The treatment of acute myocardial infarction varies with the stage of the illness. At the very onset, treatment must be directed at the pain, circulatory collapse, arrhythmias or congestive heart failure. The patient should be placed at bed rest with the head of the bed elevated. Analgesia should be obtained with a subcutaneous injection of 15 mg. of morphine sulfate, 2.0 to 4 mg. of dilaudid or an intramuscular injection of 100 mg. of demerol If delayed absorption or very severe pain become a problem, 8 to 10 mg. of morphine sulfate can be given slowly intravenously Oxygen administered by tent should be routine. If severe chest pain persists for more than 24 hours, one must consider the presence of progressive infarction, acute pericarditis or trigger areas in the myofascial structures of the chest (see chapter on Surgical Treatment for further details).

After the initial state has stabilized and pain has subsided, then other routines can be started. At all times the patient must be watched for sudden adverse changes. It has been suggested that the patient be allowed a commode at the bedside rather than a bed pan (63). Further, the armchair has been suggested as a substitute for the bed during the period of convalescence. Mitchell and his co-workers (64) indicate that the patient must be just as quiet in the chair as he is in bed The patient remains in the chair for as much of the day as he is comfortable, returning to bed when he feels too tired to sit up any longer He should be helped in and out of bed. His increase in activity is planned just as if he were in bed The diet should be fluid or soft during the first few days Then the patient may choose his usual solid diet omitting fried and fatty foods Raw fruits and raw vegetables are gas-forming and should be omitted The choice should lie mainly in the protein foods. meat, fish, fruits and vegetables. Fruit desserts should be stewed; custards and gelatin desserts are excellent Where nausea and vomiting preclude oral feeding, 5 per cent glucose in normal saline can be *given by hypodermoclysis, using hyaluronidase to help absorption,* or by vein, if given slowly Fluids up to 1800 cc should be given (65).

Bowel movements should be noted and assisted. I prefer to pay attention to the lower end of the colon only and to assist the elimination by daily enemata, suppositories or an oil retention enema. If laxatives are used, cascara sagrada in doses of 8 cc. of the aromatic mixture is the best (66). The patient is encouraged to move both his upper and lower extremities The shoulder joints should be put through their full range of motion actively or passively at least three times daily. This will both prevent and signal the onset of shoulder joint stiffness.

Smoking is interdicted during the early weeks of an acute myocardial infarction. There is experimental evidence (199) which indicates that dogs with an acute myocardial infarction show marked change in the electrocar-

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Pollock (193) used warfarin given intravenously or orally in 100 patients, 42 of whom were patients with acute myocardial infarction. An initial dose of 75 mg. by vein proved adequate to produce therapeutic hypoprothrombinemia in 83 per cent of the 21 patients so treated. Warfarin sodium was given orally as the initial dose 81 times in 79 patients. A dose of 75 mg. proved adequate in 47 instances, was insufficient for optimal effect 15 times, and was excessive in 5 cases The average maintenance dose of warfarin sodium varied from 4 mg. to 19 mg. per day in individual cases, whether given intravenously or orally. The average maintenance dose for all patients was about 10 mg. per day.

PHENYLINDANEDIONE (86, 87, 87a) is given in an initial dose of from 200 to 500 mg in 2 or 3 divided doses The maintenance dose is from 50 to 200 mg.

EFFECT OF ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTIONS The findings for 1,031 cases of acute myocardial infarction used to determine the value of anticoagulants in the treatment of this disease has been summarized by the Committee on Anticoagulants of the American Heart Association (89).

The mortality rate in the control group was 23 4 per cent, in the treated group only 16 0 per cent. In the control group 26 0 per cent of the patients developed thromboembolic complications, while in the treated group, only 10 9 per cent Both differences are statistically significant.

Study of the prognosis for thromboembolic complications indicated that, while such complications were not individually predictable, they were in general higher among the following types of patients than among their opposites: (1) those who were severely ill at onset, (2) those who were 10 per cent or more overweight, (3) those in older age groups, (4) those who had already developed one or more thromboembolic complications, (5) those who develop congestive heart failure or shock after the initial period, and (6) those with auricular fibrillation or heart block Such patients are, therefore, particularly in need of anticoagulant therapy. Significant variations in risk were not associated with sex or site of infarction

The risk of death was found particularly high for the following types of patients: (1) those age 60 and over, (2) those 10 per cent or more overweight, (3) those with a history of congestive heart failure, diabetes, arteriosclerosis or hypertension, (4) those showing persistent congestive heart failure, or shock, or definite uremia, and (5) those who developed a thromboembolic complication during their illness When patients were characterized by their status during the initial period or the first week, the following types showed a poor prognosis (1) those evaluated initially as severely ill or as poor risk cases, (2) those showing certain abnormal rhythms, particularly auricular fibrillation and heart block, (3) those with leukocyte

250 to 300 mg in a 200 mg. per cubic centimeter concentration of aqueous heparin with safety.

Wessler and Fischbein (71) describe a method for intravenous administration of heparin without repeated venipunctures by means of the use of inlying polyethylene catheters attached to rubber-capped Tuohy-Borst adapters.

Dicumarol (72-80) or bishydroxycoumarin is given usually in doses of 300 mg the first day, 200 mg. the second, and 100 mg. the third. The daily dicumarol requirement is guided by the prothrombin time. The optimum therapeutic range (67) for anticoagulant therapy is from 25 to 39 seconds (23 to 11 per cent prothrombin activity). For clinical purposes 2 to 2½ times the control prothrombin time is satisfactory if the controlled time is 12½ seconds. The usual daily requirement of dicumarol is 50 to 75 mg, but the range necessary may vary from 25 to 175 mg daily. Its effects are counteracted by a water soluble or emulsified K_1 (Mephyton) (88). Mephyton is given intravenously in doses of 50 to 100 mg.

Tromexan or biscoumacetate has a more rapid therapeutic onset than has dicumarol. The initial dose is 1500 to 1800 mg. which may be given at hourly doses of 300 mg till the entire initial dose has been given. The subsequent daily requirement varies from 150 to 900 mg. Control here has not been found to be as easy as with dicumarol.

Cumopyran or cyclocumarol is given in initial dose from 100 to 150 mg. followed by daily doses of 25 to 75 mg.

Coumadin or Warfarin is a water-soluble coumarin derivative that can be given intravenously (84, 85). The drug is prepared in ampules of 5 ml containing 25 mg., and 10 ml. containing 75 mg. The initial dose is 1 mg per kg of body weight. This produces an anticoagulant effect within 12 to 24 hours which lasts from 5 to 7 days. Shapiro (84) lists the following chemical and physiological characteristics of Warfarin.

(1) It is 75,000 times more soluble in water than dicumarol, cyclocumarol or Warfarin *per se*.
(2) It can be given intravenously.
(3) Relatively small dosage provides therapeutic hypoprothrombinemia.
(4) Initial hypoprothrombinemia appears earlier than from dicumarol or cumopyran
(5) Hemorrhagic tendency from over-dosage is less than from dicumarol.
(6) It produces no side effects as indicated in (5) above
(7) It has a high capacity to produce hypoprothrombinemia
(8) It yields a smooth extended curve of hypoprothrombinemia (expressed as prolongation of prothrombin time).
(9) It is readily counteracted by water-soluble menadione or emulsion of vitamin K1.

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counts of 20,000 ccm. or more, (4) those with rectal temperature of 103°F or more, (5) those showing a drop of either 60 mm. systolic or 40 mm diastolic or more below their usual blood pressure level, and (6) those with a maximum pulse of 120 or more. Many patients showed more than one of these unfavorable prognostic signs. After standardization for age, the following showed no conspicuous or statistically significant association with a high mortality. sex, site of infarction, a history of coronary artery disease or of anginal syndrome.

There are those who differ with the concept of Wright, Marple and Beck (89) that all patients with acute myocardial infarction should be treated with anticoagulants (such contraindications as peptic ulcer, hemorrhagic disease, etc , are accepted by both groups). Russek and his group (76, 90-92) indicate that analysis of the causes of death among "good risk" patients showed that no more than one fatality in every hundred patients could have been prevented by dicumarol if the drug were capable of preventing all thromboembolic complications. Further, the subsequent death rate from the time of admission to the hospital was only 1 2 per cent while the incidence of clinical thromboembolism was less than 1 per cent. Patients were considered to be "good risks" when none of the following poor prognostic signs were observed on the day of admission to the hospital. (1) previous myocardial infarction, (2) intractable pain; (3) extreme degree or persistence of shock, (4) significant enlargement of the heart; (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation or flutter, ventricular tachycardia, or intraventricular block, and (8) diabetic acidosis or other states predisposing to thrombosis Wright counters with the evidence that the mildly or moderately ill showed a death rate of 14 per cent in the control group as compared with 7 per cent in the treated group Further, when "good risk" cases classified by multiple criteria approximating those of Russek were separated considered, the "good risk" cases dying was below 2 per cent in both groups. Nevertheless, thromboembolic complications in the same cases remained at the high level of 20 per hundred cases in the control group as compared with 9 per hundred in the treated group.

Gold (93) takes exception to the experimental design of the American Heart Association Study (89) and indicates that the absence of a double-blind method for gathering data may weaken the argument for dicumarol Even though the alternate case method was used and excellent similarity of the control and treated groups in respect to age, sex and the severity of illness was obtained, nevertheless, conscious bias or the failure to control the subconscious bias of the physician and the emotional status of the patient opens the results to statistical criticism.

The administration of anticoagulants is not without danger Deaths from

hemorrhage have been reported (91). Others have pointed out the danger of hemopericardium (94, 95, 96) and cardiac rupture. Goldstein and Wolff (96) state that the diagnosis of hemorrhagic pericarditis should be suspected in the presence of a prolonged or persistent or recurrent friction rub, recurrence of cardiac pain, vascular collapse accompanied with distended neck veins and demonstration of pericardial effusion With over 60 *per cent of coronary artery occlusion due to subintimal hemorrhage*, Biss (97) has questioned the wisdom of administering a potentially hemorrhagic agent

It would seem, as expressed by Garb (98), that physicians can find evidence on either side to justify at the present time the administration or the withholding of anticoagulants for the treatment of acute myocardial infarction.

ANTICOAGULANTS IN IMPENDING MYOCARDIAL INFARCTION: Nichol and his group (67) have indicated that anticoagulants should be used in patients with impending myocardial infarction. This represents the clinical state of premonitory anginal pain associated with depression of the RS-T segment and/or flattening or negativity of T waves which have been called acute coronary insufficiency by Master (12) and coronary failure by Freedberg, and Blumgart and Zoll (14). Freedberg (14), contends that the practical aspect of making a diagnosis of coronary failure lies partially in the fact that since no thrombus (coronary arterial or mural) has been formed, the use of dicumarol or heparin is not indicated.

LONG-TERM ANTICOAGULANT THERAPY IN MYOCARDIAL INFARCTION Wright (99) and Nichol (67) have advocated the long term use of anticoagulants after a myocardial infarction These patients are carried ambulatory and prothrombin times are done at intervals usually of one week and occasionally of two or three weeks Foley and Wright report their experiences as follows (99a)

"Two groups of patients with myocardial infarction were studied In the first group 11 patients who had had two or more episodes of infarction were observed for 587 *patient-months without anticoagulant therapy* During this time they had 49 thromboembolic episodes, 30 were myocardial infarctions, 10 pulmonary emboli, 2 peripheral, 2 cerebral, 4 visceral, and there was 1 episode of thrombophlebitis Under anticoagulant therapy there were but three thromboembolic episodes in the subsequent period of 393 patient-months.

In the second group, 12 patients who had experienced single myocardial infarctions were treated by anticoagulants for 554 months, during which period there was one questionable thromboembolic episode."

Nichol and his group (67) began long-term anticoagulant therapy in 295 patients. One hundred twenty-five patients of this original group or 42 per

cent discontinued anticoagulant for 1 to 82 months for various reasons, only 10 because of hemorrhage. One hundred twenty-nine patients or 43.7 per cent continued the regimen, 60 of these for less than 2 years, 56 from 2 to 5 years, and 8 from 5 to over 7 years. Of these, 7 had attacks of acute myocardial ischemia without infarction usually when the prothrombin time inadvertently dropped below the effective level.

Forty-one patients, or 13 8 per cent of the entire groups, died while on the anticoagulant regimen. Nineteen autopsies were done, disclosing fresh transmural infarcts in 2 subjects, coronary thrombosis without association infarction in 2, subendocardial necrosis in 6, and subepicardial necrosis in 1. All hearts examined showed a varying degree of myocardial fibrosis and atherosclerosis of the coronary arteries with one or more sites of focal stenosis or old occlusion. Five ventricular aneurysms were found and in 2 of these, apical myocardial calcification was marked. Healed mural thrombi on the site of old infarctions were found in 1 case. In the 22 cases not autopsied, death was reported as coming suddenly in 10 patients, 3 developed signs of an acute infarction and lived only a few hours; 8 died of congestive heart failure, and 1 had a stroke, the nature of which was not determined.

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

Shock: Shock, in acute myocardial infarction, is manifested by a fall in blood pressure to levels usually below 100 mm. Hg systolic, a thready, rapid pulse, pallor, clammy perspiration, nausea, weakness and faintness (100). Due to the decrease in renal blood flow, shock may be accompanied by prerenal azotemia (119). Serum levels of non-protein nitrogen may exceed 100 mg. per cent. Shock, especially with a persistence of the lowered blood pressure for 24 hours or more, is attended with a high mortality The therapy is directed at the lowered cardiac output and peripheral vascular collapse (100-106). Such therapy includes the administration of oxygen by tent, narcotics, and vasopressor drugs (107-114) Intravenous and intra-arterial transfusions (115-118) have proven of limited value (104)

Nor-epinephrine (1-arterenol, levophed) is administered in the following manner 1 to 3 ampules of the drug (4 mg per each ampule) are placed in 1000 cc. of 5 per cent dextrose in distilled water or saline solution so that each cubic centimeter of solution contains 4 to 12 mcg. An intravenous infusion is started If the veins are collapsed, it may be necessary to "cut down" and insert a plastic catheter. A drip bulb is necessary to estimate the number of drops per minute. An average dose of 0 5 to 1 cc. (about 20 to 30 drops) per minute should maintain the blood pressure at between 80 to 100 mm. Hg. systolic. Abrupt withdrawal is inadvisable. As the patient appears to recover from shock, it is best gradually to reduce and then discontinue the drug. The duration of therapy may vary from a few hours to

about 6 days During the administration of the drug, the blood pressure should be taken at frequent intervals (from 5 minutes at the onset to hourly later on) and headache should be looked for as an indication of overdosage. The antecubital and femoral veins are preferable. Prolonged extravasation may cause local ischemia and superficial sloughing Warm packs (100) at and above the level of the needle during infusion has decreased the incidence and severity of cutaneous reactions. McGinn, Schluger and DiGregerio (201) have reported a method by which an attempt was made to prevent the possible slough secondary to inadvertent skin infiltration during the administration of levarterenol. a solution containing 5 mg. of Regitine and 125 turbidity-reducing units of hyaluronidase in 10 cc of normal saline was injected subcutaneously with a long, 22-gauge needle Their experience in three cases was highly successful

Mephentermine (107) (Wymine) may be given intramuscularly and intravenously A pressor response can be obtained from the injection intramuscularly of 15 to 35 mg at ½-hour intervals, or longer. The intravenous calls for a priming dose of 10 to 20 mg or more, following by an intravenous infusion of approximately 1 mg. per minute. Hydroxyamphetamine (Paredrine) is administered in doses of 10 to 20 mg. intramuscularly or 5 to 10 mg by vein Phenylephrine (neo-synephrine) is given in doses of 5 mg. intramuscularly or by vein (in critical problems) in dilute solution at intervals of from 15 minutes to 1 hour (100)

Aramine, levo-1-(M-hydroxyphenyl)-2-amine-1-propanol (100a) is given in concentrations of 50 to 200 mg per liter with an infusion rate of from 2 to 6 cc per minute One a weight basis, Aramine is only about 1/20 to 1/25 as potent as norepinephrine when administered by continuous infusion to patients in shocks, but blood pressure is easier to maintain at a constant level with Aramine

Acute Left Ventricular Failure and Congestive Heart Failure: Both conditions may develop during the course of acute myocardial infarction The treatment for these complications are as outlined in the section on heart failure It is worthy of note that the acutely infarcted myocardium appears to be more sensitive to digitalis and therefore some caution is warranted during digitalization for heart failure in these circumstances Digitalis, however, can be administered (100b) in the presence of acute myocardial infarction.

Cardiac Arrhythmias: Disturbances of the cardiac rhythm may occur in from 9 to 27 per cent of patients with acute myocardial infarction. Premature beats are the most common and are of importance when they occur frequently because ventricular premature contractions may lead to ventricular tachycardia and auricular premature contractions may lead to auricular fibrillation. The treatment of this and other arrhythmias have been consid-

ered in the section of disturbances of the heart beat. The prophylactic use of quinidine or pronestyl to prevent arrhythmias seems not warranted by clinical experience (120, 121).

Auricular fibrillation is the next most common arrhythmia. Prolongation of the P-R interval may occur in 16 per cent of cases; partial and complete heart block in 3.2 per cent and auricular nodal tachycardia in 0.5 to 2.0 per cent. The higher grades of block, especially complete auriculoventricular dissociation, are occasionally complicated by the Adams-Stokes' syndrome. Goldman (122) found posterior infarction to be associated with a high incidence of auricular and nodal arrhythmias (24.1 per cent) in comparison with anterior infarction (2.1 per cent).

Thromboembolism: The incidence of thrombotic and embolic lesions in cases of acute myocardial infarction (123-127) has been found to range from 5 to 6.5 per cent (123, 128) to 60 per cent (124) Hellerstein and Martin (125) studied the incidence and severity of thromboembolic lesions in 160 cases of myocardial infarction encountered in a series of 2,000 consecutive autopsies Seventy-three (45 per cent) of the 160 cases had a total of 111 thromboembolic lesions Peripheral infarcts were a main or contributory cause of death in 43 of the 160 cases. Hellerstein and Martin (125) collected 1,600 reported cases of clinical myocardial infarction and found an incidence of thrombo-emboli of 11.5 per cent Of 924 autopsied patients with acute myocardial infarction, 410 (44.0 per cent) had mural thrombi. Of 1,146 autopsied cases following myocardial infarction collected from the literature, the sites of emboli were as follows. Lungs, 23.5 per cent, brain, 7.7 per cent; kidney, 14 4 per cent, spleen, 8 8 per cent, extremities, 5 5 per cent, carotid or aorta, 0.5 per cent, and mesentery, 1.9 per cent.

The decrease in the clinical incidence of emboli in relation to anticoagulant therapy has been covered in the section on anticoagulants.

Rupture of the Ventricle: Rupture of the ventricle (128-130) causes death in about 10 per cent of all patients who succumb within the first 3 weeks after onset of acute myocardial infarction (126), with continued physical activity and persistent hypertension after infarction as the main etiologic factors. Survival for 3 weeks post-rupture has been reported (129). A loud systolic murmur and thrill simulating that heard in interventricular septal rupture is infrequently heard but may occur (128).

Rupture of the Atrium: This is a rare condition In 1954, Kohn, Harris and Gorham reported 1 case (131) and collected 79 others from the literature. No correct ante-mortem diagnosis had been made. The infarction is due more often to obliterative endarteritis of the atrial branches of the coronary arteries rather than to coronary thrombosis. The diagnosis is based on the presence of atrial infarction seen electrocardiographically followed by pericarditis and rupture and the presence of blood in the pericardial sac.

Perforation of the Interventricular Septum: Perforation of the interventricular septum (132-139) is characterized by the appearance of a prominent precordial systolic murmur and thrill usually most pronounced in the fourth and fifth intercostal spaces to the left of the sternum. Death may be sudden but there have been recorded survivals of 5 years (140) and 4½ years (134). Patients who survive the immediate episode develop progressive signs of congestive failure, predominantly right-sided The differential diagnosis from rupture of the papillary muscle is given in Table 16 (141)

Rupture of a Papillary Muscle: This occurs within the first 2 weeks after the acute myocardial infarction and is attended with a sudden onset of dyspnea, a loud systolic murmur over the mitral area, no thrill, acute pulmonary edema, and death suddenly or within a few hours (126, 141)

Aneurysm of the Heart: Schlichter, Hellerstein and Katz (142), in an analysis of 2273 cases of ventricular aneurysm in relation to the number of instances of myocardial infarctions found at necropsy which included 512 of their cases of myocardial infarction, found 332 aneurysms, an incidence of 15 per cent.

The analysis of the series revealed that an increased load put upon the left ventricle during the period of recent infarction was more important for the development of ventricular aneurysm than the presence of a large infarct or a through-and-through one The evidence of increased load was revealed by early unwarranted ambulation, the existence of hypertension and the presence of anatomical deformities, such as significant valvular

TABLE 16

DIFFERENTIAL CRITERIA OBSERVED IN RUPTURED PAPILLARY MUSCLE AND PERFORATION OF INTERVENTRICULAR SEPTUM

Ruptured Muscle	*Perforated Septum*
Murmur	
Present in about half of cases Usually systolic, may be diastolic Loudest in vicinity of cardiac apex, usually high pitched	Found in over 90% of cases Nearly always systolic, usually of softer quality Best heard in 3rd and 4th left interspace, parasternally Not transmitted to axilla
Thrill	
Has never been recorded in any instance	Found in over half of cases
Pseudorub	
Occasionally heard (13%).	Never recorded
Electrocardiographic evidence	
Usually shows exaggeration of original pattern of myocardial infarction but no unusual conduction defects	May show advanced conduction disturbances
Clinical evidence	
Left heart failure is the rule Usually death rather abruptly Acute intractable pulmonary edema the characteristic immediate sequel	Right heart failure that [illegible]

(After Craddock, W L and Mahe, C A)
Courtesy of Dr W L Craddock and *Journal of the American Medical Association* (141)

lesions or hypoplasia of the aorta. Seventy per cent of the cases with aneurysm in the series of 102 cases were shown to have had inadequate bed rest at the time of acute infarction One of the outstanding sequelae of ventricular aneurysm is the more frequent occurrence of mural thrombi and the consequent great incidence of thromboembolic phenomena

The aneurysm can be identified by fluoroscopy examination to demonstrate a localized bulge of the heart, by the presence of calcium in the roentgenogram and by a paradoxical pulsation. Electrocardiographically persistent ST elevations in the precordial leads, the residual pattern of myocardial infarction and the small R_1, deep S_2, S_3 pattern should be sought.

Two new surgical approaches have been promulgated. Niedner (143) strengthens the aneurysmal wall by placing a large flap from the skin of the leg against the aneurysm and suturing it around the aneurysm. It was used successfully in 2 patients with aneurysm of the ventricle and 1 with an aneurysm of the right auricle Bailey (144, 144a), reports a successful excision of the aneurysmal sac of the ventricle

Hiccups (145-148) Hiccup is a disagreeable symptom in acute myocardial infarction. The measures for relief are legion. They include breathing into a paper bag, the administration of quinidine, the inhalation of 5 to 10 per cent carbon dioxide with oxygen, rectal ether, ethyl chloride spray and phrenic crush.

Idiopathic, Recurrent Benign Pericarditis: Dressler (194) and Faure and Cazeilles (195) have observed febrile complications during the course of myocardial infarction with clinical resemblance to pericarditis, pleurisy and pleural effusion This complication may ensue as early as 2 weeks after the myocardial infarction. Neither the character of the pain nor serial electrocardiograms support any diagnosis of extension of the myocardial infarction.

Post Infarction, Shoulder Problems: A sequel of acute myocardial infarction which occurs in from 5 to 20 per cent of the patients is the shoulder-hand syndrome (149-167) It begins first as a painful shoulder with or without limitation of motion When it occurs on the left side during the course of an acute myocardial infarction, a problem in differential diagnosis arises between further coronary artery disease and the onset of a shoulder-hand syndrome (152).

Our studies on the somatic component of cardiac pain (166) following an acute myocardial infarction have led to the belief that one cause of painful and stiff shoulders is fortuitously placed trigger areas in the muscles of the shoulder girdle and upper extremities which persist after the initial noxious stimulus from the heart had ceased. Doert (168) has indicated that in the majority of cases of myocardial infarction and angina pectoris in history, the skin temperature is reduced on the side of radiation of the pain which he attributed to a vasoconstrictor reflex.

Roberts (169) found support for the theory that cardiac referred pain may be due to ischemia of the somatic nerves with vasospasm of their vessels in animal studies in which coronary artery ligation revealed contraction of the vasa nervorum of the left but not the right arm of animals. Reopening of these vasa nervorum occurred after release of the ligature

Based on our clinical experience, it has been our policy to observe all patients with acute myocardial infarction for pain, limitation of motion at the shoulders, and for the presence of trigger areas in the appropriate musculature associated with painful shoulders When found, these trigger areas have been treated by procaine infiltration or ethyl chloride spray It has also been our policy to have all patients with acute myocardial infarction perform daily shoulder exercises, which involve putting the shoulder joints actively through their full range of motion We believe that disabling post-infarction shoulder-hand syndromes can be prevented by daily motion of the shoulder joints instituted soon after the acute myocardial infarction has occurred, and by the elimination of myofascial trigger areas whenever pain appears in the upper extremities. Newman and his co-workers (170) and Cady (164) have also indicated the value of early motion of the shoulders in the prevention of shoulder disability in coronary artery disease.

Other modalities for treatment of painful shoulder following acute myocardial infarction have included roentgen therapy (171), physical therapy (171-173), stellate ganglion block (154), sympathectomy (174-176) and more recently, the use of cortisone and ACTH (177-179). The success of so many different modalities of treatment must depend on at least two factors. (1) spontaneous cure of the shoulder problem, and (2) variations in predominance of the sympathetic or somatic features of the shoulder-hand syndrome Where the problem is predominantly a sympathetic nerve disturbance, modalities of therapy aimed at nerve blocking, such as stellate ganglion block and sympathectomy, would be the method of choice Where somatic responses predominate, and by this we mean where there is a large degree of muscle, joint or tendon involvement, then local block therapy, roentgen therapy and physical therapy would seem to be the most effective therapeutic measures.

PROGNOSIS OF ACUTE MYOCARDIAL INFARCTION

The incidence of immediate mortality in acute myocardial infarction (death within 6 weeks) lies between 9 and 51 5 per cent for the usual series of cases as summarized by Baer, Heine and Krasnoff (180). The incidence increases with age, is greater with the second than with the first attack and is higher in those with a history of pre-existing cardiac disease. Other variables include place of treatment (home or hospital), whether a private or ward patient and the administration of dicumarol

Seasonal Incidence: Extremes of weather rather than the season *per se* is relative There is an increased frequency in the winter months in such cities as New York, Boston, Philadelphia, Pittsburgh, Cincinnati, Chicago and Rochester, Minnesota. In Dallas, Texas, however, the greatest number of infarcts occurred in the summer months. Heyer, Teng and Barris (181) summarized the month of occurrence in northern cities of 2,397 cases and found that the greatest number, 289, occurred in December. Of 1,386 cases of acute myocardial infarction occurring in Dallas, 152, the greatest number, occurred in July.

The following reasons have been given for such an association In the winter months we have. (1) increased frequency of respiratory infections; (2) increase in the body metabolism, and (3) the possible effect of vasomotor reflexes caused by cold weather. In hot climates we have: (1) an increase in cardiac output with an increase in blood volume, and (2) possible heart exhaustion through salt and water loss.

Precipitating Causes: Texon (182) reviewed 100 cases of acute myocardial infarction with particular reference to Workmen's Compensation cases He concluded that the pathologic stage of coronary sclerosis is the chief significant factor leading to coronary thrombosis There was a lack of significance of effort as a fact of the production of coronary thrombosis and acute myocardial infarction occurred with great frequency with no relation to such external factors as rest, exertion, emotional changes or non-penetrating chest trauma Master and Jaffe (183) report that the onset of coronary occlusion was associated with an unusual effort in only 2 per cent of 2,080 attacks and that the association was mainly coincidental

Other Factors in Prognosis: Mintz and Katz (184) report that pre-existing angina pectoris had little if any effect on the prognosis of recent myocardial infarction However, patients who continue to have angina or who develop it after a recent infarction have an immediately poorer prognosis The same is true for those who leave the hospital with the anginal syndrome. The character, location, radiation and duration of the pain during the attack or the location of the infarction electrocardiographically are of no prognostic significance Hypertension does not influence the mortality rate but the presence of diabetes mellitus, especially in women, does.

Thromboembolic phenomena are of grave prognostic significance in both sexes. Pulmonary and cerebral emboli are the most dangerous.

Billings, Kalstone, Spencer, Ball and Meneely (185) report that a past history of congestive heart failure was obtained in one third of their 240 patients with myocardial infarction The immediate mortality in this group of patients was 55 per cent in contrast to 30 per cent for the group in which no history of cardiac failure existed prior to the acute coronary occlusion. In the first week the likelihood of early death increases directly with the

degree of elevation with the temperature. A rapid pulse has a poor prognosis Sustained blood pressure below 90 mm Hg. especially when associated with shock have a poor prognosis. A marked leukocytosis (over 25,000 white blood cells per cu. mm.) indicates a poor prognosis while the degree of acceleration of the sedimentation rate is of no prognostic importance.

Prognosis has also been related to the level of the lipoprotein atherogenic index. Lyon in California, after a five-year study of 351 patients with myocardial infarction and 119 patients with angina pectoris reported that the myocardial infarction patients who died showed significantly higher atherogenic index values than those who survived. In our experience, taking the *individual* patient who has been followed for at least 4 years, we have found that the level of the atherogenic index as a sole objective test does not permit an accurate prognosis for each individual patient For example, according to Table 3 in Chapter 1, the average atherogenic index for normal males from ages 40 through 69 is from 73 to 75. The average atherogenic index for males with coronary artery disease from ages 40 through 69 ranges from 84 to 95 If we refer back to Table 7 in Chapter II, we find that 10 of the 17 males with coronary artery disease, 40 years of age or older, have atherogenic indices of 75 or below. Death has occurred in 2 of these male patients. Their atherogenic indices were 53 and 66. The 7 male patients with atherogenic indices above 75 are all alive, including 1 patient with a level of 153. There are 2 females in the series. One of these patients with a level of 174 died 3½ years after this test was taken. The other with a level of 85 is still alive.

Engelberg, Kuhn and Steinman (196) reported a favorable effect on prognosis of the administration of 200 mg of concentrated aqueous heparin twice weekly subcutaneously This dose is the minimum believed necessary to produce a substantially decreased average concentration of the low density serum lipoproteins. These authors gave 200 patients who had each sustained a myocardial infarction in the past alternately either heparin or 1 cc of isotonic saline. The placebo group of 81 men and 37 women (average age 61 6 years) received 2191 months of therapy (average 18 6 months per patient). There were 21 deaths due to cardiovascular disease in this control group The heparin group of 73 men and 32 women (average age 62.6 years) received 2067 months of therapy (average 19 7 months per patient) In this group there were 4 deaths due to cardiovascular disease The observed difference in deaths was found to be statistically significant ($p = .01$)

Prognosis After Surviving the Acute Attack: The effect of various factors on the long term mortality rate for 507 recent myocardial infarctions was assessed by Katz, Mills and Cisneros (186). The mortality rate was greatest

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in the first 2 months and then decreased progressively, by the end of the fifth to sixth year, 81 per cent of the patients were dead. The mortality rate for those who survived past the first 2 months was increased by the following in order of their deleterious effect. heart failure, diabetes mellitus, hypertension, abnormal electrocardiogram and angina pectoris

Sigler (187) summarized the prognosis in 1,700 cases of angina pectoris and coronary occlusion Of 1,208 patients who had one or more attacks of coronary occlusion, 878 had the attack as a first manifestation of coronary disease In 330 who had had symptoms previous to occlusion, the average duration from the onset of symptoms to the first attack of coronary occlusion was 3 9 years for males and 3 4 years for females. The longest duration was 21 years and the shortest two hours.

In 785 patients who were still alive after one or more attacks of coronary occlusion, the average duration between the first attack and the time when records were reviewed was about 4.9 years for males and 4 5 years for females About 45.3 per cent of all the males and 37 8 per cent of the females were alive 5 years or more; 10 7 per cent and 10.4 per cent, respectively, 10 years or more, and 2 1 per cent for 15 years or more.

In 423 patients with coronary occlusion who ultimately died, the average longevity after the first attack was 3.8 years for males and 3 1 years for females About 68 4 per cent of the males and 84 8 per cent of the females died within 4 years after the first attack, about 31.6 per cent of the males and 15 2 per cent of the females lived 5 years or longer, 8 8 per cent of the males and 7 2 per cent of the females, 10 years or longer, and 1 5 per cent of the males and 1 6 per cent of the females, 15 years or longer

Gainful Employment for the Patients Surviving an Acute Myocardial Infarction: Studies from many centers (188-192) have indicated that survivors from acute myocardial infarction may subsequently return to gainful employment. Some even urge that this be made a vital part of the direction of convalescence. Master *et al* (191) points out that two-fifths of their patients with myocardial infarction make a complete functional recovery, and a similar number experience only mild symptoms Sixty-seven and one-half per cent of the surviving patients were employed. The self-employed usually may return to work in over 90 per cent of instances, according to Becker and Kaufman (192). For others, adjustments between work capacity and the job must be made. We (189) have attempted to use the ballistocardiogram as a simple guide in addition to the symptoms and signs of diminished cardiac reserve We found a normal resting ballistocardiogram in a cardiac patient is very frequently associated with the capacity for moderate to marked energy expenditure An abnormal resting ballistocardiogram gave no consistent information about the patient's work capacity and was limited by the relatively higher incidence

of abnormal resting ballistocardiograms, as a rule, in the age groups over 50 years.

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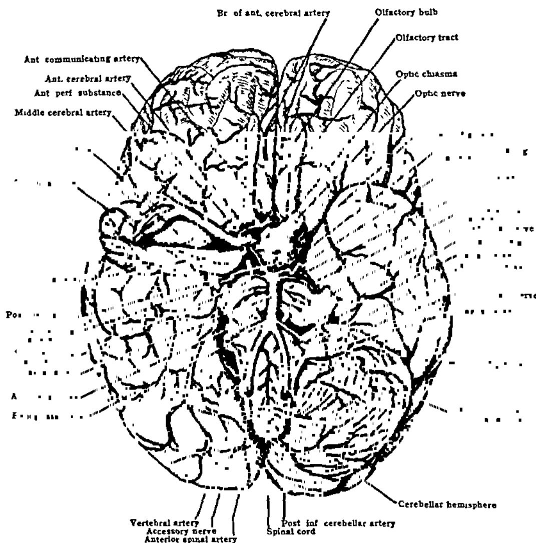


Plate V The Arteries at the Base of the Brain. (By permission from Morris' *Human Anatomy*, 11th Ed., 1953 Blakiston Division, McGraw-Hill Book Co, Inc)

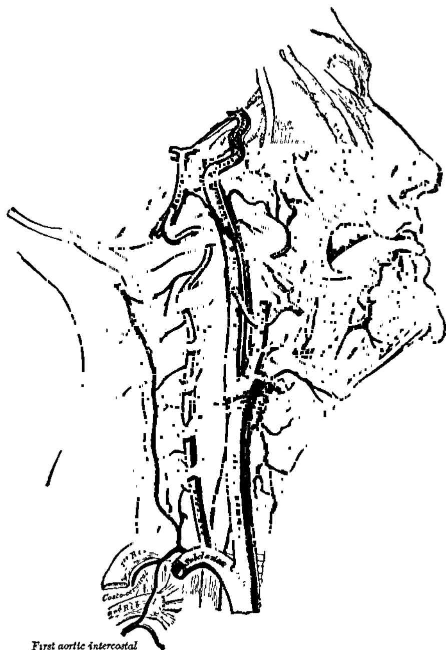


Plate VI. The internal carotid and vertebral arteries Right side (From *Gray's Anatomy*, 26th Ed., 1954. Courtesy Lea & Febiger, Philadelphia)

CHAPTER IX

Cerebral Aspects of Arteriosclerosis

BLOOD SUPPLY

CEREBRAL: The arteries of the brain (Table 17) are derived from the internal carotid and vertebral arteries They join at the base of the brain to form the Circle of Willis (Fig. 43, Plate V) The internal carotid artery arises with the external carotid from the common carotid in the neck (Plate VI). It gives off the ophthalmic artery before reaching the brain. The internal carotid enters the skull through the carotid foramen. After perforating the dura mater it terminates in the anterior, middle cerebral, posterior communicating, and anterior choroidal arteries. The anterior cerebral arteries connected by the anterior communicating artery makes up the anterior portion of the Circle of Willis. The vertebral artery arises from the first portion of the subclavian artery (Plate VI), ascends vertically to the transverse foramen of the sixth cervical vertebra, passes through it and ascends upward to enter the skull through the foramen magnum The right and left vertebral arteries join at the base of the brain to become the basilar artery. The posterior cerebral arteries which are branches of the basilar artery make up the posterior portion of the Circle of Willis. To complete the circle, the posterior communicating arteries which branch off the posterior cerebral arteries connect on either side with the internal carotid arteries

The anterior cerebral artery and its branches (Fig 44) supply parts of the frontal and parietal lobes, the corpus callosum, the septum pellucidum and the basal nuclei (caudate nucleus, putamen, internal capsule and globus pallidus). An orbital branch supplies the olfactory lobe, gyrus rectus and internal orbital gyrus The anterior cerebral artery forms an anastomosis with the posterior cerebral artery

The middle cerebral artery (Fig 44) supplies the basal ganglia and part of the frontal and parietal lobes. The anterior choroidal artery along with the middle cerebral artery (1) furnishes the main supply for the internal capsule The anterior choroidal artery arises from the internal carotid near the origin of the posterior communicating artery This last vessel supplies the hippocampal gyrus and the optic thalamus before it joins the posterior cerebral artery.

The basilar artery has the following branches· (1) pontine, (2) internal auditory, (3) anterior inferior cerebellar; (4) superior cerebellar, and (5) posterior cerebral (Plate V) The posterior cerebral artery receives the posterior communicating artery and goes on to supply the temporal and occipi-

TABLE 17

ARTERIAL SUPPLY OF THE CEREBRAL CORTEX

The Internal Carotid Artery

Branches.
1. Ophthalmic artery
2 Anterior choroidal artery
3 Anterior cerebral artery
4 Middle cerebral artery
5 Posterior communicating artery

The Anterior Cerebral Artery

Branches
1 Basal penetrating branches (Heubner's)
2 Anterior communicating
3 Prefrontal branch (for orbital surface of frontal lobe)
4 Frontopolar
5 Anterior internal frontal
6 Middle internal frontal
7. Posterior internal frontal
8 Paracentral
9 Precuneal
10 Parieto-occipital
11 Branches for the corpus callosum

The Middle Cerebral Artery

Branches, Penetrating
1 Internal Striate
2 External Striate

Cortical Branches
3 Anterior temporal
4 Ascending frontal (candelabra) with divisions
a Orbitofrontal
b Pre-rolandic
c Rolandic
d Anterior parietal
5 Posterior parietal
6 Posterior temporal
7 Terminal (supramarginal gyrus)—Probably Moniz' angular artery

The Posterior Cerebral Artery

Cortical Branches
1 Anterior temporal
2 Posterior temporal
3 Calcarine
4 Parieto-occipital

Penetrating Branches
5 Posteromesial thalamic
6 Posterolateral thalamic
7 Posterior choroidal
8 Interpeduncular
9 External peduncular
10 Quadrigeminal
11 Thalamogeniculate (posterior choroidal)

The Basilar Artery

Branches.
1. Median (for brain stem)
2 Transverse
3 Anterior inferior cerebellar
4 Superior cerebellar

The Vertebral Arteries

Branches.
1 Bulbar (for medulla)
2. Anterior spinal
3 Posterior inferior cerebellar
4 Posterior spinal

(After Ecker (3))

tal lobes (Fig 44). The anterior inferior cerebellar artery anastomoses with the posterior inferior cerebellar artery, a branch of the vertebral artery The basilar and vertebral arteries supply the posterior portion of the cerebrum, the cerebellum, mid-brain, pons and medulla.

The posterior inferior cerebellar artery supply will be described below The anterior inferior cerebellar artery supplies the caudal part of the middle cerebellar peduncle, the upper dorso-lateral limits of the medulla and the antero-inferior limits of the cerebellum The superior cerebellar artery supplies the superior cerebellar peduncle and the mesencephalic part of the spinothalamic tract, at times the medial and lateral lemnisci and the descending spinal root of the fifth nerve are also supplied in their uppermost course.

Spinal Arterial Blood Supply: The spinal branches (Fig 45) of the vertebral, intercostal, lumbar, or sacral arteries, at various spinal levels, accompany the spinal nerves through the intervertebral foramina and each divides into a dorsal and ventral radicular artery after traversing the dura mater

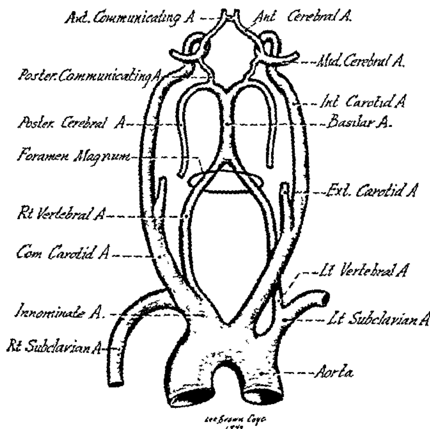


Fig 43 Diagram of the Circle of Willis with associated lateral arterial loops (After Ecker, A *The Normal Cerebral Angiogram* Springfield, Thomas, 1951.)

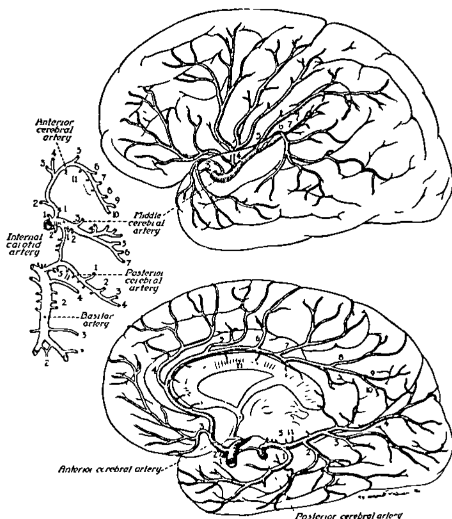


Fig 44. Arterial supply of brain The numbers correspond to branches of the appropriate artery listed in Table 17 (After Ford, F. R *Diseases of the Nervous System in Infancy, Childhood and Adolescence* Springfield, Thomas, 1952)

and arachnoid The anterior spinal artery gives off the anterior central branches which pass into the anterior median fissure and penetrates the cord The two posterior spinal arteries, one on each side, supply especially the grey substance of the dorsal horns.

In the brain stem, the anterior spinal supplies the pyramids including the decussation, the medial lemniscus, posterior longitudinal fasciculus, the hypoglossal nucleus (except higher up), the nucleus and tractus solitarius, the ventral spino-cerebellar tract in the lower medulla and olivo-cerebellar fibers at their middle crossing, the dorsal nucleus of the vagus at the level of the calamus scriptorius and the internal and ventral arcuate fibers and nucleus. The posterior spinal artery supplies the gracile and

cuneate tracts and nuclei, the inferior dorsal part of the inferior cerebellar peduncle, and sometimes the descending root of the vestibular nerve.

CEREBRAL ROENTGENOLOGY, ANGIOGRAPHY AND ARTERIOSCLEROSIS

Skull roentgen films may show calcification of the intracranial carotid artery (2) Erosion of the posterior clinoids may result from pulsations of a sclerosed basilar artery. On the whole, plain x-rays of the skull are of little value in cerebral arteriosclerosis. The cerebral vessels may be visualized radiographically (3-5) by injecting a radiopaque substance (iodopyracet U S P). Injecting the internal carotid system (3) visualizes the anterior and middle cerebral arteries (Fig 46) Injecting the vertebral basilar system reveals the cerebellar and posterior cerebral arteries (Fig. 47). The technic, complications and normal arteriographic anatomy has been presented by Ecker (3). Kaplan and Walker (6) list local hematomata, mental confusion, brain stem involvement, convulsion and even death as complications.

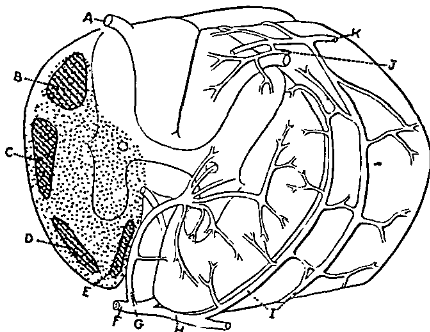


Fig 45 Schematic diagram to show the arterial blood supply of the spinal cord and areas deprived of blood by occlusion of the anterior spinal artery (stipples) A, Posterior nerve root B, Lateral corticospinal tract C, Lateral spinothalamic tract D, Ventral spinothalamic tract E, Ventral corticospinal tract F, Anterior spinal artery G, Anterior sulcal artery H, Ventral radicular artery I, Anastomosing plexus of coronal arteries. J, Dorsal radicular artery. K, Posterior spinal artery or trunk. (Courtesy of Dr A. Theodore Steegman and *Neurology* (94))



Fig 46. Age 72. Occipital arteriogram, left carotid injection with right compression Moderate arteriosclerosis. M—middle cerebral artery. P OL A—primitive olfactory artery (After Ecker, A *The Normal Cerebral Angiogram* Springfield, Thomas, 1951.)

Cerebral arteriography is not used as a rule in making a diagnosis of cerebral arteriosclerosis (7) Lima (7) makes the following points: "It will be sufficient to point out that among the various clinical aspects by which sclerosis of the cerebral arteries manifests itself, groups of symptoms sometimes appear which may be confused with a syndrome of intracranial hypertension caused by a space-occupying lesion. The occurrences of a syndrome of intracranial hypertension due to cerebral arteriosclerosis and the occasional necessity of establishing a diagnosis differentiating between this and intracranial neoplasms has already been observed by various workers

"In several of our cases, some confirmed at necropsy, the retinal alterations were indistinguishable from papilloedema of intracranial hypertension resulting from tumors, while the general arterial tension was not greatly raised. The majority of patients were between 40 and 50 years old. These patients benefit greatly from decompression, after which we have seen not

only attenuation or disappearance of the symptoms of intracranial hypertension, but also a marked lowering of the arterial blood pressure.

"In central arteriosclerosis accompanied by the syndrome of intracranial hypertension, thrombosis of the cerebral arteries, which do not necessarily give rise to focal symptoms, are sometimes encountered. We have already seen that in thrombosis of the internal carotid artery signs of intracranial hypertension may be found.

"The arteriographic images are unmistakable. The arteries appear thicker than normal, frequently being of irregular calibre and sometimes having a bossed appearance. Their course is no longer normally undulating but shows greater or lesser portions of rectilineal form. Thickened and straightened arteries are very typical of cerebral arteriosclerosis. In some arteriograms arterial thrombosis are apparent, as well as the sight of arteriosclerosis.

"Cerebral angiography with thorotrast is harmless even in advanced cases of cerebral arteriosclerosis and may be important in distinguishing intracranial hypertension due to arteriosclerosis from that from other causes,



Fig 47. Age 44. Lateral arteriogram after direct injection of right vertebral artery, normal appearance R & L VA—right and left vertebral artery. PICA—posterior inferior cerebellar artery SCA—superior cerebellar artery R & L PCA—right and left posterior cerebral artery. GCP—glomus of choroid plexus P CH A—posterior choroidal artery (After Ecker, A. *The Normal Cerebral Angiogram* Springfield, Thomas, 1951)

principally in young individuals in which the differential diagnosis may present greater difficulty."

CEREBRAL CIRCULATION AND ARTERIOSCLEROSIS

Kety and Schmidt (8, 9a) developed the nitrous oxide method for determining various dynamics of the cerebral circulation. By means of this technic (8) which depends on the rate of loss of an inert gas from the blood passing through the brain, a normal has been obtained for human cerebral blood flow of 54 cc. per 100 gm. of brain per minute, corresponding to a value of 740 cc per minute for a brain of average weight. The oxygen consumption is found to equal 3 3 cc of oxygen per 100 gm. of brain per minute, or 46 cc. per minute for the whole organ. The cerebrovascular resistance represents the resultant of all factors tending to impede the flow of blood through the brain and includes intracranial pressure, blood viscosity and organic changes in, as well as functional tone of cerebral vessels. Cerebro-

TABLE 18

COMPARISON OF CEREBRAL METABOLIC FUNCTIONS BETWEEN NORMALS AND SUBJECTS WITH CEREBRAL VASCULAR DISEASE, WITH AND WITHOUT CHANGES IN MENTAL STATUS

	Normals (33 Determinations)		*Cerebral Vascular Disease with Normal Mental Status (11 Determinations)*		*Cerebral Vascular Disease with Abnormal Mental Status (18 Determinations)*	
	Mean	*Std Error*	*Mean*	*Std. Error*	*Mean*	*Std Error*
Cerebral blood flow (ml / min /100 gm brain)	65	2 1	54*	2 7	40†	1 6
A-V O_2 difference (vol %)	6 1	0 14	7 58*	0 39	7 10*	0 3
A-V *glucose difference* (mg %)	9 9	0 42	11 6	0 9	10 6	0 78
Cerebral O_2 utilization (ml O_2/min /100 gm brain)	3 79	0 09	4 00	0 17	2 87†	0 1
Cerebral glucose utilization (mg glucose/ min /100 gm brain)	6 2	0 26	6 2	0 56	4 40†	0 43
Arterial pressure (mm *Hg*)	83	.	133*	.	131*	
Cerebrovascular resistance (mm Hg/ml blood/100 gm brain/ min) ..	1 3	0 04	2 5*	0 11	3 3†	0 18
$\frac{\text{A-V glucose}}{\text{A-V } O_2}$ ratio	1 67	0 06	1 53	0 09	1 53	0 1

* Significant variation from normal
† Significant variation from normal and from group with normal mental status
Significant P values < 0 01

$$\text{Std Error} = \sqrt{\frac{\frac{\epsilon x^2 - (\epsilon x)^2}{n}}{n-1}} \Big/ \sqrt{n}$$

(Courtesy Dr Peritz Scheinberg and *American Journal of Medicine* (9))

vascular resistance is measured in units of pressure head necessary to cause a unit flow of blood through the brain, the average normal value is 1.6 mm. Hg per cc. of blood per 100 gm. of brain per minute.

In cerebral arteriosclerosis, the cerebral blood flow was found by Kety (8) to be 41 cc./100 gm./min, the cerebral oxygen consumption to be 2.3 cc./100 gm./min, and the cerebrovascular resistance to be 3 0 mm. Hg. per cc./100 gm /min The first two components of cerebral circulation are therefore decreased and the last, increased Scheinberg (9) (Table 18) compared the cerebral metabolic function between normals and subjects with cerebral vascular disease, with and without changes in mental status. As one can see from Table 18, those patients who had no alterations in their mental status had significantly lower cerebral blood flow, higher arteriovenous oxygen differences and higher cerebrovascular resistance than normal young persons. Cerebral oxygen and cerebral glucose utilizations were normal. The subjects with abnormal mental status resulting from cerebral vascular disease had significantly lower cerebral blood flows, cerebral oxygen and glucose utilizations and higher cerebrovascular resistances than those with normal mental status or than normal young subjects. These groups represent two stages in the natural progression of cerebral vascular disease

Heyman and his group (10) and Fazekas (11) found reduced cerebral blood flow and oxygen consumption in patients with cerebrovascular accidents or with encephalomalacia caused by arteriosclerosis and hypertension. Heyman (10) noted that the administration of 85 to 100 per cent oxygen to patients with cerebrovascular accidents caused a reduction of cerebral blood flow, whereas 50 per cent oxygen produced little change in this function In view of the vasoconstrictive effect of inhalation of 100 per cent oxygen, Heyman (10) urged avoidance of the use of this concentration of gas in patients with cerebrovascular accidents

CEREBRAL ARTERIOSCLEROSIS

Arteriosclerosis of the cerebral arteries (12-15) is the second commonest cause of death due to vascular disease, the first, of course, being coronary atherosclerosis. Blumenthal, Handler and Blache (16) feel that arteriosclerosis of the intracranial arteries differ in pathologic characteristics from that of arteries elsewhere in the body because the cerebral arterial plaques enlarge and extend into the vessel wall as well as into the lumen The growth of the plaque into the vessel leads to atrophy of the muscle of the media, so that the plaque may lie directly against a granulating adventitia. This is the reason for the high frequency and rupture of and hemorrhage from cerebral arteries Destruction of the internal elastic lamella by the plaque and focal atrophy of the media lead to aneurysm.

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	Normals (33 *Determinations*)		*Cerebral Vascular Disease with Normal Mental Status* (11 *Determinations*)		*Cerebral Vascular Disease with Abnormal Mental Status* (18 *Determinations*)	
	Mean	*Std Error*	*Mean*	*Std Error*	*Mean*	*Std Error*
Cerebral blood flow (ml/min/100 gm brain)	65	2.1	54*	2.7	40†	1.6
A-V O_2 difference (vol %)	6.1	0.14	7.58*	0.39	7.10*	0.3
A-V glucose difference (mg %)	9.9	0.42	11.6	0.9	10.6	0.78
Cerebral O_2 utilization (ml O_2/min/100 gm brain)	3.79	0.09	4.00	0.17	2.87†	0.1
Cerebral glucose utilization (mg glucose/min/100 gm brain)	6.2	0.26	6.2	0.56	4.40†	0.43
Arterial pressure (mm Hg)	83		133*	.	131*	
Cerebrovascular resistance (mm Hg/ml blood/100 gm brain/min)	1.3	0.04	2.5*	0.11	3.3†	0.18
$\frac{\text{A-V glucose}}{\text{A-V } O_2}$ ratio	1.67	0.06	1.53	0.09	1.53	0.1

* Significant variation from normal
† Significant variation from normal and from group with normal mental status
Significant P values < 0.01

$$\text{Std Error} = \sqrt{\frac{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}{n-1}} \Big/ \sqrt{n}$$

(Courtesy Dr Peritz Scheinberg and *American Journal of Medicine* (9).)

dilatation therapy actually improves the function of physiologically impaired or non-functioning brain cells." The mechanism of action is unknown. Scheinberg (39) concluded that nicotinic acid does not cause cerebral vasodilatation

Hall (36) administered priscoline orally in doses of 25 mg. four times daily for 4 weeks. The psychotic symptoms were not benefited.

Levy (28) found the best combination to be an elixir containing 0.2 gm. of metrazol and 100 mg of nicotinic acid per 4 cc with compound elixir as the vehicle It was given in doses of 4 cc three times a day. This elixir produced physical improvement in the patients both objectively and subjectively and produced a marked improvement in their behavior

CEREBROVASCULAR ACCIDENTS

Arteriosclerosis is the most common cause of cerebral thrombosis (40). The vast majority of hemorrhages into the brain are the result of rupture of arteriosclerotic vessels Cerebral emboli are frequently associated with auricular fibrillation or coronary thrombosis with mural thrombi Coronary thrombosis and cerebral thrombosis may occur together Central nervous system manifestations have been noted in acute myocardial infarction (41-49). Hemiplegia has been described as the presenting symptom of acute myocardial infarction (43, 44). Bean and Read (43) pointed out that hemiplegia and acute myocardial infarction occurring in the same patient might be: (1) independent of each other, (2) the cerebral disorder might be an embolic sequel of dislodging a ventricular mural thrombus, or (3) shock resulting from the acute cardiac disorder might be associated with cerebral ischemia, especially when arteriosclerosis of vessels in the brain was advanced

As for arteriosclerosis and intracranial aneurysms, in the older age groups arteriosclerosis is a causative as well as a contributory factor to the formation of intracranial aneurysms but the vast majority of the aneurysms in the sub-arachnoid space in all age groups are due to congenital weakness of the wall Of 572 cases of intracranial aneurysms reported by McDonald and Korb (50), arteriosclerotic changes in the vessel wall were found on pathologic examination in 49 5 per cent

Despite this, the role of arteriosclerosis in the etiology of saccular aneurysms is still disputed (50-53) Hamby (52) states, "It would seem that if arteriosclerosis were the chief cause of intracranial aneurysms, the preponderance of lesions should be found located on the vertebral-basilar segment of the circle of Willis, since in practically all reported series these vessels are the most heavily involved by arteriosclerosis Precisely the contrary is true, hence it is likely that some factor other than arteriosclerosis is responsible for the majority of intracranial aneurysms"

Aneurysms may compress cranial nerves resulting in palsy (2, 54, 55)

tions are frequently noted. Depressive feelings, emotional lability, and a fear of impending failure of physical and mental powers are often prominent features, and outspoken suicidal tendencies are by no means uncommon. Explosive outbreaks of weeping or laughter are occasionally encountered, usually in cases with gross neurologic alterations. Ideas of mistreatment or jealousy and transient persecutory ideas may be observed, but persistent, well developed paranoid pictures rarely occur.

Neurologic changes are noted in the majority of cases at one time or another. Hemiplegia or hemiparesis is found in about half the cases. Occasionally, a Parkinson's syndrome is present as is aphasia, pseudobulbar involvement, or convulsive seizures. Cardiovascular alterations are common. As a rule, the blood pressure is high. Minor urinary abnormalities are often found and occasionally azotemia.

The acute confused or delirious state which frequently initiates the psychosis may last for weeks or months Death results in about half of the cases Remissions, when they occur, may last for months or years, until terminated fatally by apoplexy or myocardial infarction or failure.

Allen (17) reports from the New York Hospital, Westchester Division, on the virtues of hospital care for such patients. "A systematized routine, with proper nursing care, adequate nutritional intake and proper elimination, frequently conduces to a state of adjustment in which the patient can function comfortably without supportive drugs, sedatives or special diets. Many patients come to the hospital suffering from psychosis with cerebral arteriosclerosis who have been taking barbiturates, aminophyllin, paraldehyde and demerol, and have been on low-protein, salt-free diets Within a few days all these aids can, in most cases, be discontinued." Besides routine care, such patients in whom evidence of cerebral damage is not marked and who are deeply depressed, are often relieved of the depression by electroshock therapy (17, 27). But, cautions Allen (17), the cerebral-arteriosclerotic patient should first have the opportunity to respond adequately to the usually more conservative methods of psychiatric therapy.

Several drugs have been administered in the treatment of cerebral arteriosclerotics with psychosis (28). These include histamine (29), nicotinic acid (29), metrazol (30-35), priscoline (36), and reserpine (39a).

Fong (31) treated 35 patients for 180 days with doses of oral metrazol 0.1 to 0.2 gm four times daily and noticed a decrease in anxiety, agitation, emotional lability, irritability, and fatiguability with better sleep habits and general physical improvements. Favorable results on similar doses were reported by Andosca (37) and by Chesrow, Giacove and Wosika (30) Convulsive seizures have been reported by Treyathan (38) on the usual dose of metrazol.

Nicotinic acid has been given alone and in combination with histamine by Moore (29). He believes that "intravenous histamine-nicotinic acid

held as if frozen in a chorea-athetoid posture. (6) If the lesion affects the pulvinar, and especially the lateral geniculate body, homonymous quadrantic and hemianopic defects will be found in the opposite visual fields

If the main trunk of the artery is thrombosed, both the thalamus and the occipital lobe are destroyed and the signs will be those usually known as the thalamic syndrome, together with homonymous hemianopsia Should the thalamogeniculate branch be involved, only the thalamic syndrome will develop, if the calcarine branches become thrombosed, a contralateral homonymous hemianopsia is the only clinical sign Thrombosis of smaller branches may give rise to parts of these syndromes.

Mella (80) recorded a case of complete blindness with rapid but not instantaneous onset due to advanced arteriosclerotic disease involving both posterior cerebral arteries with infarction of visual cortex. This was proved at autopsy

Wagman (81) reports an instance of simultaneous bilateral homonymous hemianopsia (without sparing of the inovular) due supposedly to posterior cerebral artery thrombosis The site of disease in this syndrome is the visual cortex and subjacent white matter The visual cortex is located in the mesial aspect of the occipital lobes, where it occupies the lip and floor of the calcarine fissures. Such blindness is designated "cortical blindness" as distinguished from loss of vision due to lesions elsewhere in the visual pathway. As a rule "sparing of the macula" (preservation of the central vision) occurs, presumably due to collateral circulation from the middle cerebral artery.

VASCULAR LESIONS OF THE BRAIN STEM

The brain stem (pons, mid-brain, medulla) is supplied by the basilar and vertebral arteries Details of syndromes of brain stem involvement are given in Table 20

Posterior Inferior Cerebellar Artery (82, 83, 84): The structures involved (84, 84a) include, according to Lewis, Littman and Foley (84)

(1) Medullary extension of the lateral spinothalamic tract, carrying pain and temperature sensation from the opposite side of the body.

(2) Medullary extensions of the anterior and posterior spinocerebellar tracts, carrying deep sensibility impulses to the cerebellum.

(3) Descending root and nucleus of the trigeminal nerve, conveying pain and temperature sensation from the ipsilateral side of the face

(4) Nucleus ambiguus, which supplies the striated muscles of the pharynx, larynx and soft palate via the IX and X nerves

(5) Reticular formations, containing the sympathetic pathway from the hypothalamus to the spinal cord, and also the respiratory center.

(6) Sensory nuclei of the glossopharyngeal and vagus nerves and the dorsal nucleus of the vagus.

(7) Restiform body (inferior cerebellar peduncle).

(2) Ideomotor apraxia affecting the arm.

(3) Psychomotor disturbances in the upper limb of the same side as the paralyzed leg (these comprise forced grasping and groping).

(4) With the dominant hemisphere affected, mental confusion, clouding of consciousness and aphasia may occur.

Bilateral thrombosis may occur. Schuster (quoted by 72) recorded such *a case proved by necropsy The two strokes were suffered within 4 years.* He became paralyzed in both legs and demented. He was completely disoriented The left forearm was held tightly across the chest, with the fist clenched Both legs were very weak, with tendon jerks increased, especially on the left side. The Babinski responses were in extension

Middle Cerebral Artery (15, 27, 75-78, 144). It is the occlusion of this artery, and especially of the lenticulo-optic branch, that produces the common picture of hemiplegia as seen in cerebro-vascular complications of atherosclerosis. Besides contralateral hemiplegia, there may be hemianesthesia and homonymous hemianopsia Further, aphasia occurs when the dominant hemisphere is involved

The *internal capsule is also supplied by the anterior choroidal artery* and interference with its circulation results in signs similar to that with a middle cerebral artery occlusion. The anterior choroidal has recently come in for more attention because of the operative procedure (ligation) for the treatment of Parkinsonism (158).

Posterior Cerebral Artery: Brock (79) described the thalamic syndrome as follows. (1) a diminution of loss of sensation on the opposite half of the body, including limbs and face (2) Pain sense exhibits a most peculiar change. The individual often has pains in the affected half-body or in a part of it, as a limb or even one-half of the face These pains are often intractable and have a burning, agonizing character; they are apt to be persistent and subject to exacerbations. Objective examination often reveals a hemihypalgesia or hemianalgesia associated with a distressed feeling difficult for the patient to describe (thalamic hyperpathia). (3) There is hemiataxia dependent on sensory losses or on disruption of cerebello-rubro-thalamic connections The ataxia is apt to be greater in the upper than in the lower limb. (4) A mild hemiparesis exists which is due to involvement of the internal capsule by the lateral spread of the lesion One may also encounter a lower mimetic facial paralysis on the opposite side with preservation of the voluntary innervation (5) *Involuntary movements* are frequently present on the opposite side, they are of the chorea-athetoid type. The chorea-athetoid movements are usually more marked in the upper extremity. A tremor which may have a very large amplitude, is apt to be elicited on movement (*intention tremor*). *It is very likely dependent* upon disruption of rubro-thalamic connections. A curious condition of the opposite hand has been noted in thalamic lesions; the fingers and hand are

held as if frozen in a chorea-athetoid posture. (6) If the lesion affects the pulvinar, and especially the lateral geniculate body, homonymous quadrantic and hemianopic defects will be found in the opposite visual fields

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(6) Sensory nuclei of the glossopharyngeal and vagus nerves and the dorsal nucleus of the vagus

(7) Restiform body (inferior cerebellar peduncle)

TABLE 20

THE SYNDROME OF THE BRAIN STEM

(In this table the most important syndromes of the brain-stem are analyzed The reader should keep in mind the "alternating" character, i e , the ipsilateral versus the contralateral signs)

Site of Lesion	Name of Syndrome or Special Etiology	Involvement of Parts Supplied			
		By Ipsilateral	And Producing Ipsilateral	By	And Producing Contralateral
		Medulla			
Decussation of pyramids	Hemiplegia cruciata	Pyramidal fibers to lower limb (Spinal accessory nerve incomplete)	Spastic paralysis of lower limb (Flaccid paresis and atrophy of sternomastoid and trapezius [partial] muscles)	Pyramidal fibers to upper limb	Spastic paralysis of upper limb
Tegmentum lower third	Jackson	Nucleus of 12th N	Flaccid paralysis and atrophy of tongue		
		Nucleus of 11th N (Very *large* area)	Flaccid paralysis and atrophy of sternomastoid and trapezius (partial) muscles		
		Nucleus of 10th N (nucleus ambiguus)	Flaccid paralysis of soft palate and vocal cord		
Tegmentum lower third	Schmidt	Nucleus of 11th N	Flaccid weakness and atrophy of sternomastoid and trapezius (partial) muscles		
		Nucleus of 10th N	Flaccid paralysis of soft palate and vocal cord		
Tegmentum lower third	Avellis	Nucleus of 10th N (nucleus ambiguus)	Flaccid paralysis of soft palate and vocal cord	Median lemniscus	Loss of gnostic sensibility with ataxia
				Spinothalamic tract	Loss of pain and temperature in trunk and limbs
Mesolateral tegmentum lower third	Tapia	Nucleus of 12th N	Flaccid paralysis and atrophy of tongue		
		Nucleus of 10th N (nucleus ambiguus)	Flaccid paralysis of vocal cord		

Mesial-basitegmental	Babinski-Nageotte	Inferior cerebellar peduncle	Hypotonus and dysynergy	Pyramid	Hemiplegia
		Descending sympathetic tract in reticular substance	Miosis, Enophthalmos, ptosis	Medial lemniscus	Loss of gnostic sensations with ataxia in limbs and trunk (face spared)
Mesial-basitegmental	Cestan-Chenais Thrombosis of vertebral artery	Inferior cerebellar peduncle	Hypotonus and dysynergy	Pyramids'	Hemiplegia
		Descending sympathetic tract in reticular substance	Miosis, enophthalmos, ptosis	Medial lemniscus	Loss of gnostic sensations with ataxia in limbs and trunk (face spared)
		Nucleus ambiguus (of 10th)	Flaccid paralysis of soft palate and vocal cord		
Mesial-basitegmental bilateral	Thrombosis of anterior spinal artery	Fibers of 12th N*	Flaccid paralysis and wasting of tongue	Pyramids*	Spastic quadriplegia (sparing face)
				Medial lemnisci'	Bilateral (four limbs and trunk) loss of gnostic sensation with ataxia
Dorsolateraltegmental	Thrombosis of posterior inferior cerebellar artery	Spino-cerebellar afferent tracts	Hypotonus and dysynergy	Spinothalamic tract	Loss of pain and temperature in limbs and trunk
		Descending spinal tract of 5th nerve	Loss of pain and temperature in face		
		Nucleus ambiguus (of 10th)	Flaccid paralysis of soft palate and vocal cord		
		Descending sympathetic tract	Miosis, enophthalmos, ptosis		
			Pons		
Caudal basitegmental	Raymond and Cestan	Inferior cerebellar peduncle	Hypotonus and dysynergy	Pyramid	Hemiplegia
				Medial lemniscus	Loss of gnostic sensation and ataxia
		Posterior longitudinal fasciculus	Paralysis of lateral gaze or		Contralateral ocular deviation
Caudal Medial-basitegmental	Thrombosis of basilar artery medial pontine branches (Millard-Gubler-Foville type)	Emergent VI fibers	Paralysis of external rectus (internal squint)	Pyramid	Hemiplegia
		VII fibers	Facial paralysis	Medial lemniscus	Loss of gnostic sensation with ataxia
		Posterior longitudinal fasciculus	Paralysis of lateral gaze or	.	Contralateral ocular deviation

* May be spared
' Only one may be involved

TABLE 20 (*Continued*)

Site of Lesion	*Name of Syndrome or Special Etiology*	*Involvement of Parts Supplied* — *By Ipsilateral*	*And Producing Ipsilateral*	*By*	*And Producing Contralateral*
Caudal basimesial	Millard-Gubler type	Emergent VI fibers	Paralysis of external rectus (internal squint)	Pyramid	Hemiplegia
		or Emergent VI and VII	Above with facial paralysis		
Caudal Transverse tegmental		VIII Vestibular and	Nystagmus	Medial lemniscus	Loss of gnostic sensation with ataxia
		VIII Cochlear	Deafness		
		VII	Facial paralysis		
		VI	Paralysis of external rectus (internal squint)		
		V (Descend sensory tract)	Loss of pain and temperature on face		
		Inferior cerebellar peduncle	Hypotonus and dysynergy		
		Posterior longitudinal fasciculus	Paralysis of lateral gaze or	. . . .	Contralateral ocular deviation
Mid pons lateral tegmental		Motor and upper sensory nuclei of V	Paralysis of jaw muscles (jaw deviation) Hemi-anesthesia of face	Medial lemniscus (incomplete)	Partial defect in gnostic sensation with ataxia
		Superior cerebellar peduncle	Choreo-athetosis or tremor of limbs	Spinothalamic tract	Loss of pain and temperature (face, trunk, limbs)
Mid pons, mesial basi-tegmental	Thrombosis of mid-portion of basilar artery			Pyramid (cortico-nuclear V, VII, and XII)	Hemiplegia including face and tongue
				Median lemniscus	Loss of gnostic sensation
				Spinothalamic tract	Loss of pain and temperature in limbs, trunk and face
High pons basi-tegmental				Posterior longitudinal fasciculus	Fixed conjugate gaze
				Pyramid and (cortico-nuclear VII and XII)	Hemiplegia including face and tongue

High pons mesial basal	Thrombosis of basilar artery			Pyramid (complete) Pyramid (partial) Cortico-nuclear fibers to VII and XII on both sides	Complete hemiplegia on one side Partial hemiplegia on the other Bifacial and bilingual paralysis with dysarthria and dysphagia
High pons, basi-tegmental	Pontile syndrome of Foville	Posterior longitudinal fasciculus Facial nucleus Fibers of VI	Paralysis of lateral gaze Facial paralysis External rectus palsy (internal squint)	Pyramid	Hemiplegia
			Midbrain		
	Syndrome of the superior cerebellar artery Lateral-tegmental	Superior cerebellar peduncle or cerebellar lobes	Tremor (involuntary movements), hypotonus, dysynergy	Spinothalamic	Defective pain and temperature appreciation in face, body and limbs
	Peduncular mesial basal			Pyramid	Hemiplegia
	Paralytic syndrome of Foville			Oculocephalogyric fibers	Paralysis of oculocephalogyric movements with resultant turning of head and eyes to side of lesion, due to unopposed action of centers on healthy side
	Convulsive syndrome of Foville			Pyramid Oculocephalogyric fibers	Convulsive movements of limbs Turning of head and eyes toward convulsed limbs (i.e., away from the side of the lesion)

TABLE 20 (Continued)

Site of Lesion	Name of Syndrome or Special Etiology	Involvement of Parts Supplied			
		By Ipsilateral	And Producing Ipsilateral	By	And Producing Contralateral
	Tegmental peduncular syndrome of Benedikt	Emerging fibers of 3rd nerve	Ptosis and paralysis of some or all of the muscles supplied by 3rd nerve (external strabismus) Dilated pupil	Red nucleus (Medial lemniscus)	Ataxic tremor (Loss of gnostic sensation with ataxia)
	Basi-peduncular syndrome of Weber	Emerging fibers of 3rd nerve	Ptosis and paralysis of some or all of the muscles supplied by 3rd nerve (external strabismus) Dilated pupil	Pyramid	Hemiplegia, including face and tongue
Subthalamic	Mesial-basal Subthalamic syndrome of Foville	Subthalamic cortico-nuclear fibers	Bilateral paralysis of vertical gaze	Pyramid	Hemiplegia, including face and tongue

(Modified from Jelliffe and White, after Brock, S (79))
Courtesy of Dr Samuel Brock and Williams & Wilkins Co

(8) Deiters' (lateral vestibular) nucleus

The occlusion of the posterior inferior cerebellar artery will produce softening in the lateral part of the medulla. The medial side of the medulla, which includes the hypoglossal nucleus and nerve, the mesial fillet, the posterior longitudinal bundle and the pyramidal tract is not affected because

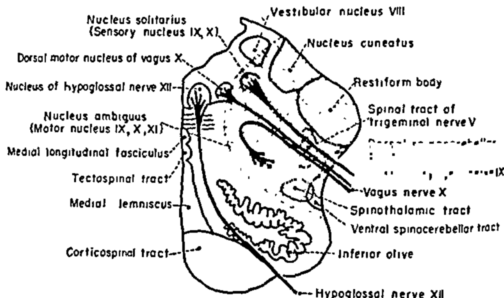


Fig. 48. Cross section of the medulla at mid-olivary level (Redrawn with permission from Purves-Stewart *The Diagnosis of Nervous Diseases*, 9th Ed Baltimore, Williams & Wilkins, 1945 Courtesy of Dr E F Foley and *Annals of Internal Medicine*)

this area receives its blood supply from the upper branch of the anterior spinal artery which arises from the vertebral artery (Fig 48).

The classic picture (Tables 21 and 22) is one of a sudden onset, without loss of consciousness The patient experiences dizziness and headache and falls toward the side of the lesion. The patient notices inability to swallow (nucleus ambiguus of the tenth nerve) and numbness or paresthesia of the contralateral side of the body and the homolateral side of the face Diminution or loss of pain and temperature sensibility may be noted along the distribution of the trigeminal nerve on the side of the lesion and on the contralateral side of the body below the head Ataxia of the homolateral extremities is present (restiform body and cerebellum). There is homolateral paralysis of the soft palate and the muscles of deglutition with deviation of the uvula way from the side of the lesion. There is often a sympathetic disturbance, causing homolateral Horner's syndrome with miosis, enophthalmos, ptosis of the lid and decreased perspiration. Nystagmus (vestibular nuclei) and homolateral facial paresis (nucleus facialis) may

TABLE 21

SYMPTOMS IN 28 PATIENTS WITH THROMBOSIS OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY

Complaint	*Present*	*Denied*	*Not clearly recorded*
Acute onset	27	1 (subacute)	0
Vomiting	20	8	0
Dysphagia	20	5	3
Giddiness	23	2	3
Vertigo	22	1	5
Falling	14	11	3
Paresthesias	21	2	5
Dysphonia (including hoarseness)	19	5	4
Hiccough	14	7	7
Diplopia*	16	4	6
Motor weakness	20	2	6
Headache	16	5	7

*Two patients were blind prior to the stroke
(*After Lewis, G N, Littman, A, and Foley, E F (84)*)
Courtesy of Dr Edmund Foley and *Annals of Internal Medicine*

also be present. Impairment of pain and temperature is found on the opposite side of the body (spinothalamic tract) from the lesion

Anterior Inferior Cerebellar Artery occlusion results in a clinical picture not unlike that of posterior inferior cerebellar artery occlusion. According to Merritt (75) the difference lies in that "the main sensory nucleus of the fifth nerve and the nuclei of the seventh and eighth cranials are affected instead of the nucleus ambiguus of the tenth nerve and the descending nucleus of the fifth nerve"

Superior Cerebellar Artery occlusion produces a syndrome like that of the anterior inferior cerebellar artery with the addition of homolateral involuntary choreiform movements because of damage to the brachium conjunctivum. Loss of hearing and facial paralysis are less frequent and the loss of pain and temperature sensation involves the entire half of the body on the opposite side, with the face included (75) Thrombosis (85) results in a lesion of the spinothalamic tract in the midbrain and the superior cerebellar peduncle There is ipsilateral incoordination of skilled voluntary movements with loss of pain and temperature of the opposite half of the face and body Onset is sudden and there is gradual improvement.

Basilar Artery: The onset is sudden and not preceded by tangible causal factors (86-93, 93a) The first symptom is usually headache, dizziness, confusion or coma Difficulty in speaking and hemilateral paresthesia occur in a large proportion of the cases. Common findings are pupillary abnormalities, disorder of ocular movements, facial palsy, hemiplegia and/or quadraplegia and ipsilateral extension plantar reflexes Cranial nerve palsies

and contralateral hemiplegia may be combined. It is common for temporary improvement, lasting hours or days, to occur during the course of the illness. In the majority of cases death takes place from 2 days to 5 weeks.

Millikan and Siekert (90) have described a syndrome of intermittent insufficiency of the basilar arterial system The symptoms include loss of vision, double vision, ptosis, clouding of consciousness, confusion, unconsciousness, hemiparesis and hemiplegia, dysarthria, dysphagia, sensory phenomena in the face or one extremity or half of the body, vertigo, tinnitus, vomiting, unsteadiness and headache. Although they admit that each of the above symptoms is nonspecific, that the same symptom on opposite sides of the body in definite attacks (that is, hemiparesis on the left side and at other times on the right) associated with such phenomena as dimness of vision throughout the visual fields, dysarthria, dysphagia or

TABLE 22

NEUROLOGIC ABNORMALITIES IN 28 PATIENTS WITH THROMBOSIS OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY

	Present	*Absent*	*Not Clearly Recorded*
1. *Horner's Syndrome*	24	3	1
2. Impairment of pain and temperature perception			
(a) *Ipsilateral face and contralateral trunk*	20		
(b) Contralateral face and contralateral trunk	4		
(c) Contralateral trunk *only*	3		
Total	27		
3 Cerebellar signs (exclusive of nystagmus)	17	7	4
Nystagmus	18	8	2
4 Cranial nerves			
(a) Diplopia	16	4	6*
(b) Facial weakness	19	7	2
(c) Palatal paralysis	19	6	3
(d) Dysphonia (including hoarseness)	19	5	4
(e) Dysphagia	20	5	3
(f) Hiccough	14	7	7
5. Hemiparesis			
(a) Ipsilateral	12		
(b) Contralateral	18		
Total	20	6	2
6 Babinski's sign			
(a) Ipsilateral	5		
(b) Contralateral	6		
	11	13	4

*Two patients were blind prior to these episodes
(After Lewis, Littman, and Foley (81))
Courtesy of Dr Edmund Foley and *Annals of Internal Medicine*

vertigo, make the diagnosis probable. Anticoagulant therapy (91) is particularly effective here.

Vertebral Artery: Occlusion of a single vertebral artery may produce symptoms as listed in Table 20, under Medulla. These include the Babinski-Nageotte syndrome, the Cestan-Chenais syndrome, Avellis syndrome, and Schmidt's syndrome.

Ford (168) describes the following symptoms in vertebral artery thrombosis.

a) Where it penetrates the dura.
   1) Contralateral hemiplegia without involvement of the face.
   2) Analgesia and thermanesthesia on the homolateral side of the face.
b) At the level of the origin of the posterior inferior cerebellar artery.
   1) Hemiplegia without facial weakness on opposite side.
   2) Symptoms of occlusion of posterior inferior cerebellar
c) At cephalic extremity.
   1) Hemiplegia on oppposite side without facial weakness
   2) Hemianesthesia on the opposite side of the body.
   3) Paralysis of the tongue on the same side
   4) Probably also symptoms of occlusion of the posterior inferior cerebellum artery.

Pseudobulbar Palsy (40, 75). The clinical syndrome known as pseudobulbar palsy does not occur only as a result of cerebral arteriosclerosis but, in the cases where it does, it is the result of either many areas of softening in fortuitous portions of the brain or of thrombi in both internal capsules which occur at different periods in the course of cerebral disease. The term pseudo is applied to this lesion because it does not involve the bulb directly but the supranuclear pathways that involve cortical innervation of the bulbar nuclei Only voluntary motor power is effected On the other hand, progressive bulbar atrophy is the result of lower motor neurone involvement and may result in fasciculation and muscle atrophy.

It is known that the muscles which have to do with voluntary motion of the arms and legs have their innervation from just a single side of the brain and this is usually the contralateral side. However, the muscles of the tongue, lips, mouth and pharynx which are concerned with talking, swallowing and chewing are innervated bilaterally. It follows then that a lesion of one side of the brain which involves the internal capsule may result in a hemiplegia of the opposite side and yet not result in disturbances of chewing, swallowing, etc. Lesions in both internal capsules, even though separated by several years in occurrence may, however, result in the syndrome of pseudobulbar palsy

The clinical features include:

1. Difficulty in speaking
2. Difficulty in swallowing.
3. Difficulty in chewing.
4. Spontaneous outbursts of weeping or laughter.
5. Repetition of words.
6. Concomitant unilateral or bilateral hemiplegia.
7. Occasional regurgitation of food through the nose.
8. Absence of atrophy of the tongue and other muscles of the face.

A special situation in the treatment of these patients arises because of the problems of mastication and dysphagia. Feeding may have to be carried on through a nasal tube In other respects, the treatment in the acute stage is as for the usual hemiplegia

SPINOVASCULAR ACCIDENTS

Anterior Spinal Artery (94-103)· The lesion consists of softening of the anterior two-thirds of the spinal cord Clinically the onset is sudden and apoplectic. There is a rapid onset of paraplegia, accompanied by sensory disturbances There are also sphincter disturbances, reflex alterations, and trophic changes, with the greatest disability appearing in the early hours or within several days

Symptoms depend on the location and the extent of the disease. In the medulla (104), thrombosis of the anterior spinal artery consists of a spastic tetraplegia wth anesthesia below the level of the lesion Sensory disturbances are directly related to the degree of vascular interference. Tendon reflexes are hyperactive, muscle tonus is increased, and plantar reflexes are extensor in type

In the cervical region, there is a flaccid paralysis of the upper extremity, and a spastic diplegia of the lower extremities Pain and temperature sense is lost below the level of the lesion Touch remains intact

Lesions in the thoraco-lumbar area result in spastic diplegia of the lower extremities, with escape of the arms. Sensory dissociation, like that occurring in cervical cord lesions, is also found here. Lesions may be unilateral Lesions in the lumbar region cause a flaccid paralysis Also, sensory changes of the type described above appear Retention and then dribbling, bowel incontinence, and trophic ulcer may complicate the situation.

Posterior and Other Spinal Arteries: Lesions in other arteries of the spinal cord fail to produce a clear-cut syndrome, such as occurs in disease of the anterior spinal artery. Occlusions of the posterior spinal artery have less occasion to produce extensive disturbances than that which results from similar lesions in the anterior spinal artery because of abundant anastomoses of the ipsilateral vessel.

Bilateral thrombosis of the posterior spinal artery may produce paralysis, sensory loss, girdle pains, anesthesia, loss of all reflexes, bowel and bladder paralysis, and decubitus

DIFFERENTIATION OF CEREBRAL HEMORRHAGE *FROM CEREBRAL THROMBOSIS*

Spontaneous intracerebral hemorrhage may result from an atheromatous aneurysm of the cerebral arteries (52, 105-111) or from simple rupture of an arteriosclerotic vessel associated with hypertension. The differential diagnosis of spontaneous intracerebral hemorrhage from cerebral thrombosis is important because such therapy as stellate block, heparinization, or dicumarolization, which some advocate in thrombosis, would be contraindicated in hemorrhage (Table 23).

Aring and Merritt (112) found arteriosclerosis, as evidenced by examination of the peripheral vessels and those of the retina, occurs more frequently and is more advanced in cases of cerebral thrombosis, no evidence of arteriosclerosis was found in 10 per cent of their cases with cerebral hemorrhage, as compared with 1 per cent of those with cerebral thrombosis Stiffness of the neck was found in 55 per cent of patients with cerebral

TABLE 23

Clinical Differential Diagnosis of Apoplexy

Diagnostic Features	*Thrombosis*	*Hemorrhage*	*Embolus*
Age of onset	65 (senescence)	50 (middle age)	10 (adolescence youth)
Previous indications	History of diabetes, nephritis, syphilis, arteriosclerosis Prodromal symptoms headache, vertigo, poor memory	History of hypertension	History of cardiac disturbance (mitral stenosis, fibrillating heart, coronary disease, endocarditis)
Nature of onset	Slow (days), during rest, often during sleep	Rapid (hours), during activity (straining, lifting)	Fulminating (minutes), during rest or activity
Clinical Features	No loss of consciousness	Loss of consciousness (coma), signs of increased intracranial pressure and shock	Rapid loss of consciousness
Cerebrospinal fluid	Clear	Blood-tinged	Pleocytosis, moderate increase in red blood cells
Prognosis	Fair. 30% die first week	Grave. 30% die first day, 60% die first week	Good, depending upon etiology

(From Harris, T. H and Towler, M D (51).)
Courtesy of Dr Titus H Harris and Paul B Hoeber, Inc

hemorrhage and in only 7 per cent of those with cerebral thrombosis The bilateral occurrence of the Babinski sign was found twice as often in cerebral hemorrhage (28 per cent) as in cerebral thrombosis (15 per cent). They believe the differential diagnosis between cerebral hemorrhage and cerebral thrombosis can usually be made during life A thorough analysis of the history, together with the results of the physical and neurologic examinations, and of the examination of the cerebrospinal fluid, should make the differentiation in nearly 100 per cent of the cases.

As to incidence, Millikan and Moersch (113), in a clinical study of 223 patients who had acute focal cerebrovascular lesions and who were observed during a period of 2 years, 82 5 per cent had cerebral infarction without embolism, 10 8 per cent had cerebral embolism accompanied by infarction, and 6 7 per cent had focal intracerebral hemorrhage. Factors that influenced the prognosis in these patients were age, existence of hypertension or cardiac disease or both, speed of onset of the symptoms and whether the lesion was simple infarction (15 per cent of mortality), embolism (50 per cent), or hemorrhages (73 per cent).

In a series of 143 cases selected from the records of the Montreal Neurological Institute, Dekaban and McEachern (114) analyzed the relation of spontaneous subarachnoid hemorrhage, intracerebral hemorrhage and intracranial aneurysm Since postmortem examination was not obtained in all cases, the criteria for selection were. (1) the condition had to be proved by lumbar puncture, arteriogram, operation, or autopsy; (2) onset of hemorrhage must have occurred within four days prior to admission, and (3) traumatic cases were excluded. Of 56 patients with subarachnoid hemorrhage of undetermined cause, 17 showed moderate arteriosclerosis. Twenty-six of 30 ruptured aneurysms were of the congenital, berry type; the remaining four were fusiform and of arteriosclerotic origin. About three-quarters of the ruptured aneurysms were located in the anterior half of the circle of Willis.

TREATMENT OF HEMIPLEGIA

At the present time, the immediate treatment of the patient with an acute cerebrovascular accident involves·

1. General treatment.
2. Steps to differentiate between cerebral thrombosis, hemorrhage and embolus which involve the differential points discussed above. Of aid in this diagnosis will be the history of onset, the spinal fluid findings and the cardiac status (rhythm and electrocardiographic findings) Stellate block has its best indication in cerebral embolism, anticoagulants in thrombosis.
3. Rehabilitation Program The following is suggested while the patient is in bed (118):

a) A foot board or posterior leg splint to prevent foot drop.
b) Sand bags to prevent outward rotation of the affected leg.
c) A pillow in the axilla of the involved upper extremity to minimize adduction and internal rotation.
d) Quadriceps muscle setting of the involved lower extremity to maintain muscle strength
e) Sitting in bed to re-establish balance.
f) Speech therapy if patient is aphasic
g) Pulley therapy for shoulder.

General Treatment (115, 116, 117): The immediate treatment of the patient in coma is the same for cerebral thrombosis and hemorrhage. The patient should be kept at rest with the head slightly elevated. Sedation may be given for restlessness. chloral hydrage, 1 gm, or paraldehyde, 4 to 8 cc. by mouth, or paraldehyde, 2 to 4 cc. intramuscularly as necessary. Catheterize every 8 hours if necessary. Enemata after the first 2 days may be used. Turning of the patient plus antibiotics may prevent respiratory complications or pressure sores. A clear airway is paramount

Stellate Ganglion Blocks: The use of stellate ganglion block (119) in the management of cerebral vascular accidents is based upon its action through interruption of vasoconstrictor impulses in decreasing or obliterating spasm that may be present following cerebral embolism, thrombosis, hemorrhage or other focal cerebral lesions

Scheinberg (9) found no significant change in cerebral blood flow, oxygen utilization of cerebrovascular resistance in unilateral stellate ganglion block performed on 19 subjects which included normal subjects and patients with cerebrovascular disease. In 3 of these patients the stellate ganglia were blocked within 2 to 12 hours after an acute cerebral thrombosis. Scheinberg believes that stellate ganglion block might even produce a decrease in cerebral blood flow by directing more blood to the skin and subcutaneous tissues of the face. However, the success of this therapy points out that reflex cerebrovascular spasm in response to embolism or thrombosis may occur and may be mediated by this sympathetic innervation.

Shenkin *et al* (120) studied the cerebrovascular function after bilateral stellectomy, including 1 patient with cerebral arteriosclerosis and found a significant decrease in cerebrovascular resistance following operation.

Gilbert and De Takats (121) find the best results in embolism and thrombosis. This method is not advised in the presence of hemorrhage. The controversy about the usefulness of stellate block still goes on, some for its use and others against (9, 119, 121-132). De Takats (133) in late 1954, concluded that from a study of the literature and from personal observations on 55 patients with apoplexy treated with stellate block, that there was

no way of selecting the suitable case, and that only half of the patients derived benefit from the procedure.

Drugs: Aminophyllin, a good coronary vasodilator, causes a striking and highly significant increase in cerebrovascular resistance which results in a decrease in cerebral blood flow (134). Aminophyllin, in intravenous doses of 0.5 gm., instead of acting as a vasodilator, produces a marked constriction of cerebral vessels with cerebral anoxia as reflected in the constant and striking decrease in cerebral venous oxygen content.

Nicotinic acid given intravenously to patients with cerebrovascular disease produced no significant changes in cerebral blood flow, oxygen utilization, or cerebrovascular resistance (39).

Russek and Zohman (135) reported successful management of vascular encephalopathy by the use of large oral doses of papaverine (up to 1.2 gm. daily). These results were based on observations of 46 patients with encephalopathy associated with hypertensive disease and cerebrovascular disease without hypertension. The rationale for the use of papaverine was based on the knowledge that: (1) papaverine is a coronary vasodilator, and (2) in encephalopathic episodes, a state of cerebral angiospasm exists. Scheinberg and associates (136, 137) were able to demonstrate, in a group of patients which excluded those with known cerebrovascular disease, that intravenous papaverine (180 mg.), resulted in a 24 per cent increase in cerebral blood flow and a 28 per cent decrease in cerebral vascular resistance.

Dihydroergocomine (DHO-180) was found to have no significant effect on the time-course of rehabilitation of 10 hemiplegic patients (138, 139).

Prostigmine (140) and histamine (141) have been tried in the past but are rarely used today.

Anticoagulant Therapy: The best case for the use of anticoagulants has been made by Wright and his group (142, 142a). It is recommended for cerebral thrombosis only as an endeavor to: (a) prevent propagation of the original thrombus which might occlude additional branches of the involved artery, thus increasing the size of the infarcted area, (b) prevent the development of additional thrombi in other vessels, (c) encourage the more rapid disintegration of the original thrombus by the enzyme systems in the blood, which may have a freer action in the presence of adequate anticoagulant therapy.

The risks which must be evaluated include (a) an erroneous diagnosis of thrombosis or embolus, when the condition is actually hemorrhage which may be aggravated by anticoagulants. A spinal tap should therefore be performed on every patient who is to be given anticoagulant therapy to possibly establish the differential diagnosis. It is still not known whether anticoagulant therapy, to be effective, must be given the first day of the

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placed in position by the bed, back to back, with sufficient room for the patient to stand between. He is taught to grasp the back of one chair with the good hand and the other chair with the affected hand It may be necessary to lace the affected hand to the back of the chair with bandage. After a few days of standing, when the patient has recovered his balance, he may be taught to walk using the chairs in a reciprocal motion As the right hand pushes the chair forward, the left foot is advanced, and when the left hand pushes the chair forward, the right foot is advanced. It may be necessary for the nurse or member of the family to help the patient push the chair forward on the affected side. Utilizing a smooth surface, such as linoleum on the kitchen floor, the patient can be taught to become ambulatory again.

"We have found it necessary to use short leg braces in a greater percentage of cases than has been reported elsewhere Approximately 50 per cent of our patients with hemiplegia are fitted with short leg braces to correct the toe drop so common with this disability. The double-bar, short leg brace with a 90 degree stop is used in the majority of the patients. For some women, or if the drop is not complete, the patient may be fitted with the spring type of brace which extends from the heel of the shoe up the posterior of the leg to the calf For cosmetic reasons this brace is preferred by many patients

"The patient is then taught to climb stairs and curbs and how to get in and out of an automobile and bus.

"Last, the patient must be taught personal care activities, such as to dress himself, and, if necessary, how to tie a tie or shoelaces with one hand.

"In our experience, the arm and hand are the last to return in function,

TABLE 24

COMPARISON OF FUNCTIONAL STATUS IN PATIENTS WITH HEMIPLEGIA AT AVERAGE TIME 4 4 AND 4 5 MONTHS AFTER CEREBROVASCULAR ACCIDENT

	After Treatment of Rehabilitation Service *Combined*	*Direct Admission to Rehabilitation Service from Home or Other Hospital (No Treatment)*
No of patients	17	18
Average time of analysis after cerebrovascular accident (months)	4.5	4 4
A D L (% normal)	78 4	33.0
Muscle strength (% normal)		
Arm and forearm	41.7	25 6
Hand	36 2	22 5
Thigh and leg	60 0	39 3
Foot	26 1	17.4
Range of motion (passive) (% normal)		
Arm and forearm	85 5	81 2
Hand	96 6	90 2
Thigh and leg	91 3	82.5

stroke or whether a few days can pass while the differential diagnosis is being made; (b) the aggravation of hemorrhage in the cerebral infarct; (c) hemorrhage elsewhere in the body.

Wright and McDevitt (142) treated, with anticoagulants, 19 patients who suffered from cerebral vascular accidents, which were believed to be on the basis of embolization arising from a mural thrombus secondary to myocardial infarction or to thrombosis of cerebral arteries. Eight of these patients suffered 13 myocardial infarctions preceding other thromboembolic episodes, some thromboembolic episodes did occur at therapeutic levels Thirteen of the 19 patients were hypertensive. In 248 months and 13 days before anticoagulant therapy, 48 thromboembolic episodes occurred, 25 of which were cerebral. During 287 patient months of anticoagulant therapy the same patients suffered only eight thromboembolic episodes, of which two were cerebral.

Rehabilitation: The use of physical therapeutic and rehabilitation measures in the treatment of hemiplegia is well established (138, 139, 143-148). The therapeutic success is measured in the time-course of rehabilitation, which is defined as the shortest interval in days between the onset of treatment and the greatest achievement in range of joint motion, muscle strength, and performance of tasks of daily living.

We have offered evidence that a formal program of rehabilitation can achieve this (Table 24) A comparison of the averages of the results of tests in the three aforementioned modalities of 18 untreated hemiplegic patients were compared with a group of 17 patients treated on the rehabilitation program. The two groups were studied at an average time of 4.4 and 4 5 months, respectively, after the onset of the hemiplegia A very striking difference is noted in the results of the activities of daily living (A.D.L.) testing The untreated patients, on the average, were able to accomplish 33 per cent of the activities, whereas the group which had passed through the formal rehabilitation program had an average accomplishment of 78 4 per cent. The treated group also demonstrated a consistently greater muscle strength and range of motion, although these differences are less striking than for the activities of daily living It would appear, from these facts, that, although the simple passage of time may result in a certain amount of spontaneous recovery or improvement in some hemiplegic patients, the institution of an active program of rehabilitation definitely has a favorable influence on the prognosis with regard to return of function and, particularly, to the development of self-sufficiency in the activities essential to daily life.

The active rehabilitation of the hemiplegic, after the phase in bed is ended, is stated by Covalt (144):

"The patient is now ready to be taught to sit on the edge of the bed and next to stand by the side of the bed. Two ordinary kitchen chairs can be

placed in position by the bed, back to back, with sufficient room for the patient to stand between. He is taught to grasp the back of one chair with the good hand and the other chair with the affected hand. It may be necessary to lace the affected hand to the back of the chair with bandage. After a few days of standing, when the patient has recovered his balance, he may be taught to walk using the chairs in a reciprocal motion. As the right hand pushes the chair forward, the left foot is advanced, and when the left hand pushes the chair forward, the right foot is advanced. It may be necessary for the nurse or member of the family to help the patient push the chair forward on the affected side Utilizing a smooth surface, such as linoleum on the kitchen floor, the patient can be taught to become ambulatory again.

"We have found it necessary to use short leg braces in a greater percentage of cases than has been reported elsewhere Approximately 50 per cent of our patients with hemiplegia are fitted with short leg braces to correct the toe drop so common with this disability The double-bar, short leg brace with a 90 degree stop is used in the majority of the patients For some women, or if the drop is not complete, the patient may be fitted with the spring type of brace which extends from the heel of the shoe up the posterior of the leg to the calf. For cosmetic reasons this brace is preferred by many patients

"The patient is then taught to climb stairs and curbs and how to get in and out of an automobile and bus.

"Last, the patient must be taught personal care activities, such as to dress himself, and, if necessary, how to tie a tie or shoelaces with one hand

"In our experience, the arm and hand are the last to return in function,

TABLE 24

COMPARISON OF FUNCTIONAL STATUS IN PATIENTS WITH HEMIPLEGIA AT AVERAGE TIME 4.4 AND 4.5 MONTHS AFTER CEREBROVASCULAR ACCIDENT

	After Treatment of Rehabilitation Service *Combined*	*Direct Admission to Rehabilitation Service from Home or Other Hospital (No Treatment)*
No of patients	17	18
Average time of analysis after cerebrovascular accident (months)	4.5	4.4
A.D.L. (% normal)	78.4	33.0
Muscle strength (% normal)		
Arm and forearm	41.7	25.6
Hand	36.2	22.5
Thigh and leg	60.0	39.3
Foot	26.1	17.4
Range of motion (passive) (% normal)		
Arm and forearm	85.5	81.2
Hand	96.6	90.2
Thigh and leg	91.3	82.5

and, in some cases, the function never returns. The family should be told that the prognosis for a completely paralyzed arm and hand is not good.

"Following these rather simple procedures, the majority of patients with [illegible] are capable of part-

A follow-up study of 208 hemiplegics discharged in 1949 from the Physical Medicine and Rehabilitation Service of the New York University Bellevue Medical Center is given by McCoy and Rusk (149).

Ninety per cent received definite net functional benefits from rehabilitation, but only 50 per cent had good rehabilitation ratings, i.e., were found to be making maximum use of the abilities they had left in a way satisfactory to them and the community.

Neither sex, age, economic status, education, type of disability, nor even time lapse between disability and rehabilitation appeared to be strong factors in this situation. It was found in this study that a time lapse of 15 years or more did not prevent the individual from learning to use what he had left successfully, the loss was in losing abilities he might have developed and saved with earlier rehabilitation, and in the length of time required for treatment

The striking finding of the study was the incidence of acute psycho-social problems among this group. Of the aspects considered, individual motivation and social opportunity appeared as the determining factors of successful rehabilitation Moreover, the experience of this group strongly indicated the underlying generic character of problems of social opportunity in this situation. There was, reasonably, a hard core of psychiatric problems among these cases, but, for the great majority, opportunity "to live and work with what is left" was the immediate problem to be solved. Understanding the social situation was a basic condition for definitive diagnosis of personality problems in many of these cases

Parkinson's Syndrome: Arteriosclerosis is the cause of Parkinson's syndrome in some patients (72, 150) The syndrome is a chronic degenerative disease of the extrapyramidal system. In the presenile and senile types, vascular arteriosclerotic changes are sometimes observed. The disease is characterized by enfeeblement, rigidity and tremor, and is usually slowly progressive It often affects the one hand first and causes a pill-rolling motion which ceases on intention and is usually absent during sleep Later the patients exhibit sialorrhea, seborrhea, speech difficulties, muscle incoordination, hyperhidrosis and oculogyric crises and finally become bedfast because of the rigidity of muscles and trophic joint disturbances Difficulty in swallowing is often a problem.

The early phase of parkinsonism, according to Edwards (150), is difficult to evaluate. Patients often have muscle pain which may be confused with arthritic or neuritic pains Fingers and arms may become stiff and only later

be recognized as a progressive change, rather than a fault of the weather or of the tools and instruments used in work As tremor and more rigidity develop in one or both arms, the tremor may extend to neck, head and legs. The tremor is coarse, can be controlled for a time by intention, and is usually absent during sleep Diminution of the pendulousness of the arms in walking is an early sign in extra-pyramidal rigidity. The mask-like expressionless face, and the tendency to turn the entire trunk slowly rather than turning the head only when looking to the side, are characteristic of the late stages.

DRUG THERAPY: The following drugs in the given dosage are useful in the treatment of arteriosclerotic parkinsonism (150-155, 169, 170).

1 Cogentin: 1 to 2 mg. on retiring or twice a day. Good for tremor. Excellent for spasm

2 Artane: 2 to 5 mg two or three times daily. Good antispasmodic. Fair anti-tremor action.

3 Pagitane: 1 25 to 2.5 mg twice daily. Good anti-spasmodic. Excellent anti-tremor action

4 Parsidol 25 to 100 mg. three times daily. Excellent for tremor.

5 Rabellon· ½ to 1 tablet three times daily. Fair antispasmodic.

6 Thephorin. 25 mg. three or four times a day.

7. Scopolamine. 0 3 to 0 6 mg two or three times a day Excellent anti-tremor but causes drowsiness

8 Dexedrine· 2 5 or 5 mg twice a day for fatigue and weakness

9. Thorazine 25 to 50 mg upon retiring.

10 Benadryl. 25 to 50 mg three or four times a day.

Using this list of drugs and Edwards' recommendations (150), the following plans of therapy may be followed

Mild or early involvement Thephorin, 25 mg. three or four times daily. If sufficient relief is not obtained, add Rabellon, 1 tablet three times daily Artane, 1 mg two or three times daily, may or may not be needed.

Moderate or severe involvement. Artane, 2 mg two or three times daily plus Thephorin, 25 mg four times daily, and Rabellon, 1 tablet, three times daily may be tried. Pagitane, 1 25 mg. three to four times daily may be tried

Another plan includes Parsidol, 50 mg on arising, 25 mg. at noon and 25 mg. at dinner time, Pagitane, 1¼ mg three times daily after meals and Cogentin 2 mg on retiring

Weinberg (156) treated arteriosclerotic parkinsonism with a combination of heparin and testosterone Drooling was relieved. Testosterone alone did little or nothing Tremors were not improved by this combination

Surgical therapy (157-164) Operative intervention has usually been reserved for paralysis agitans of postencephalitic rather than of arteriosclerotic origin. Pyramidotomy (48, 106, 159, 160) or section of the U fibers of the motor cortex (165) have been used with questionable success

In 1953 (157, 158) Cooper described a new surgical technic for this disorder. It consisted of surgical occlusion of the anterior choroidal artery in order to selectively decrease or obliterate the blood supply to certain intracerebral structures dependent upon this vessel for their blood supply. The structure most affected by this occlusion was the medial segment of the globus pallidus. Such occlusion produced varying degrees of alleviation of resting-type, or pill-rolling tremor. The most significant result of the procedure was the reduction of rigidity. Cooper (157) has also described a technic for intracerebral injection of procaine in the globus pallidus prior to operation in order to select patients properly. A small trephine opening is used, the area for injection well located; about 1 5 cc. of 0.5 per cent procaine is injected and repeated with slight variations in depth, observations are made on changes in tremor and rigidity. In 8 instances in which this was done, tremor and rigidity in the contralateral extremities were markedly reduced or totally alleviated within two to five minutes after the first injection.

Doshay (162) feels that anterior choroidal ligation has no place in geriatric parkinson patients.

Popkin (166) has advanced the idea that constant parkinsonian tremors may be on the basis of twisted, tortuous cerebral arteries, with a rhythmic torsion movement induced with each heart beat. The diseased anterior choroidal artery with each thrusting or twisting movement induced by increase in the blood volume, impinges against the adjacent brain tissue This mechanical impact is stated to be the explanation of parkinsonian tremor and might be the explanation for the subsidence of tremor following ligation of the anterior choroidal artery.

Other Therapy. Psychotherapy, occupational therapy and physiotherapy can be combined with drug therapy. Doshay (155) feels that some patients need no outside physiotherapy since they are fully capable of maintaining a good state of muscle health The very rigid require regular and frequent physiotherapy. Doshay (170), in a Panel Meeting on Therapeutics on Parkinsonism, stated that "The real challenge to therapy arises when the rigidity begins to spread from one side of the body, across the neck and trunk, to the other side. When rigidity becomes bilateral and the patient is increasingly slowed up, *then if treatment is neglected*, tragic secondary changes develop that do not belong intrinsically to Parkinson's disease but to factors of disuse. In other words, if a patient does not use a rigid arm, it inevitably becomes tighter and shorter. In due time, fibromyositis sets in The muscle fibers are replaced by connective tissue which becomes scar tissue. Scar tissue does not relax, nor does it contract. A scarred muscle is difficult to use, hence it is employed less and less The less such muscles are employed, the shorter they become so that a vicious cycle is formed. Contractures

develop that lead to deformities of the hands, arms and legs. At the knees, for example, the hamstrings shorten so that the knees become bent and the body is thrown forward into a propulsive posture At the ankles, the tendo Achilles shortens, so that the patient is forced to walk on his toes and the entire body is thrown forward into a propulsive and festinating gait The weight of the trunk is greater than any support it receives from the legs, so that gravity helps to pull the patient down and there are frequent falls and fractures of an arm or leg. As a safety precaution, the family confines the patient to a chair or bed, so that in due time the patient becomes bedridden and invalidism sets in.

"Contractures constitute a severe handicap to the Parkinson patient. They can be prevented to a large extent in almost every patient, by rigid attention to proper medication, regular physiotherapy and continual exercise on the part of the patient Effective treatment would prevent deformities and disabilities, or at least would postpone them for many years and give the patient free limbs and a capacity for self-care and work."

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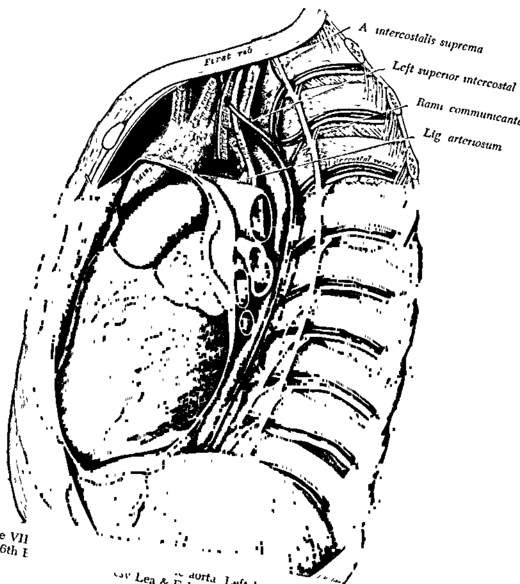


Plate VII ... aorta Left lateral aspect (From Gray's Anat-
omy, 26th E ... sy Lea & Febiger, Philadelphia)

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CHAPTER X

Aortic Aspects of Arteriosclerosis

BLOOD SUPPLY

THE THORACIC aorta (Plate VII), arises from the left ventricle of the heart, proceeds cephalad as the ascending aorta, arches backward and to the left as the arch of the aorta, then descends on the left side of the vertebral column as the descending aorta The innominate artery comes off the aortic arch, and bifurcates into the right common carotid and right subclavian arteries. The abdominal aorta (Plate VIII) starts at the diaphragm and ends at about the level of the body of the fourth lumbar vertebra by dividing into the right and left common iliac arteries The common iliac arteries divide into the external iliac and the hypogastric arteries.

ARTERIOSCLEROSIS OF THE THORACIC AORTA

The diagnosis of arteriosclerosis of the thoracic aorta as indicated by Reich (1), is made by.

1 The presence of arteriosclerosis elsewhere in the body

2 Ringing quality of the second aortic sound

3. Harsh systolic murmur over the aortic area (On occasion, systolic hypertension is present)

4. Roentgenologic interpretation (Fig 49), including calcification of the descending portion of the aorta (2) (Fig 6) Calcification of the knob and descending portion of the aorta is to be contrasted with calcification of the ascending portion (Fig 50), which is luetic in origin

a. Increase in width and expansile pulsations of the thoracic aorta on fluoroscopic examination

b Tortuosity, elongation, and accentuation of the aortic knob

c The descending aorta is displaced to the left of the spine

OCCLUSION OF THE AORTA

Occlusion of the aorta may be embolic or thrombotic in origin Embolic phenomena may be secondary to auricular fibrillation or mural thrombi in myocardial infarction In autopsied cases with myocardial infarction, emboli (1) were found to involve the aorta in 0 5 per cent whereas 5 5 per cent proceeded to the extremities, 14 per cent to the kidneys, 7 7 per cent to the brain and 1 9 per cent to the mesentery

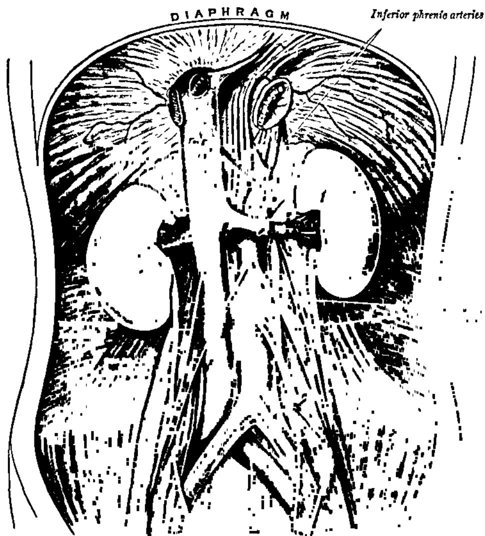


Plate VIII. The abdominal aorta and its branches (From *Gray's Anatomy*, 26th Ed, 1954. Courtesy Lea & Febiger, Philadelphia)

Aortic Aspects of Arteriosclerosis

BLOOD SUPPLY

THE THORACIC aorta (Plate VII), arises from the left ventricle of the heart, proceeds cephalad as the ascending aorta, arches backward and to the left as the arch of the aorta, then descends on the left side of the vertebral column as the descending aorta The innominate artery comes off the aortic arch, and bifurcates into the right common carotid and right subclavian arteries. The abdominal aorta (Plate VIII) starts at the diaphragm and ends at about the level of the body of the fourth lumbar vertebra by dividing into the right and left common iliac arteries The common iliac arteries divide into the external iliac and the hypogastric arteries.

ARTERIOSCLEROSIS OF THE THORACIC AORTA

The diagnosis of arteriosclerosis of the thoracic aorta as indicated by Reich (1), is made by:

1. The presence of arteriosclerosis elsewhere in the body.
2. Ringing quality of the second aortic sound
3. Harsh systolic murmur over the aortic area. (On occasion, systolic hypertension is present.)
4. Roentgenologic interpretation (Fig 49), including calcification of the descending portion of the aorta (2) (Fig 6) Calcification of the knob and descending portion of the aorta is to be contrasted with calcification of the ascending portion (Fig 50), which is luetic in origin

a Increase in width and expansile pulsations of the thoracic aorta on fluoroscopic examination

b Tortuosity, elongation, and accentuation of the aortic knob

c The descending aorta is displaced to the left of the spine

OCCLUSION OF THE AORTA

Occlusion of the aorta may be embolic or thrombotic in origin Embolic phenomena may be secondary to auricular fibrillation or mural thrombi in myocardial infarction In autopsied cases with myocardial infarction, emboli (1) were found to involve the aorta in 0 5 per cent whereas 5 5 per cent proceeded to the extremities, 14 per cent to the kidneys, 7 7 per cent to the brain and 1.9 per cent to the mesentery



Fig 49. Roentgenogram of the heart of a 63-year-old white male with arteriosclerotic heart disease, effort angina and previous myocardial infarction demonstrating a dilated aorta

THROMBOARTERIOSCLEROSIS OF THE ABDOMINAL AORTA

Arteriosclerosis of the aorta may exist without symptoms and may only be detected by the presence of calcification in the arterial wall on roentgen examination (2) A syndrome of thrombotic obliteration of the aortic bifurcation was first mentioned by Graham in 1814 and firmly established clinically by Leriche and Morel (3). There is a gradual occlusion of the lower abdominal aorta near the bifurcation, extending downward into the common iliac arteries (Fig. 51). It sometimes originates in one common iliac artery, later extending to the other iliac artery and to the aorta The process may extend upward to involve the renal and superior mesenteric arteries.

The following symptoms have been noted most commonly (4-13)

Low back pain and pain in the hips and thighs may be induced by walking (intermittent claudication). Fatigue of the lower extremities may occur after standing and occasional distress in the lower extremities may

appear even at rest. Coldness and pallor of the lower extremities may appear. Inability to maintain erection of the penis may ensue

The following physical signs have been noted most commonly by Giberson *et al.* (4): Arterial pulsations are diminished or absent in the lower abdominal aorta and below the bifurcation of the aorta. Oscillometric readings in the legs are reduced. Coldness and varying degrees of pallor are seen in the feet and legs. Atrophy of the lower extremities occurs occasionally. Partial or complete obstruction of the lower part of the abdominal aorta can be demonstrated by an aortogram



Fig 50 Lateral roentgenogram of the chest of a 75-year-old white male with luetic heart disease, luetic aortitis and aortic insufficiency, illustrating calcification of the ascending aorta. (Courtesy X-ray Department, Beth Israel Hospital, New York)



Fig. 51. Thrombotic obliteration of the aortic bifurcation—Leriche Syndrome (Translumbar Abdominal Aortogram). A 48-year-old male with intermittent claudication
Film exposed following 2 to 3-second injection o
an 18 gauge needle inserted via translumbar ro
are outlined as are the renal arteries. (Courtesy

The technic of aortography used by De Wolfe and the Cleveland Clinic group (5) is given in detail:*

"If the aorta is completely blocked in its terminal portion, a small amount of an opaque medium inserted through a single needle provides sufficient

* Courtesy of Dr. De Wolfe and by permission of *Circulation* (9·1, 1954)

concentration for an excellent aortogram. If, however, the block is a partial one in an iliac vessel, the blood flows rapidly past the injecting needle and more of the opaque medium must be injected per unit of time to provide a concentration sufficient for a distinct, diagnostic roentgenogram. Since it is impossible to ascertain the location and the extent of the block beforehand, we have found that the two needle-two syringe method, which insures a satisfactory film, is preferred in all cases.

"The patient is placed in a prone position with blanket rolls under each side of the chest and is lightly anesthetized with Sodium Pentothal administered by arm vein. Unless the aorta is suspected to be to the right of the midline, the left side of the patient is prepared with antiseptic from the midline to the flank and from the tenth dorsal vertebra to the gluteal cleft. This area is blocked off with sterile drapes. An 18-gauge, six-inch needle with stylet is inserted through the skin, four finger-breadths lateral to the midline at the desired level. Since less of the opaque medium is lost if the needles are inserted just below the renal arteries, the level of the second or third lumbar vertebra is used unless contraindicated The needle is carried down to the lateral wall of the vertebral body which is grazed, as in doing a lumbar paravertebral block. It is inserted one to one and one-half inches farther until the aortic wall is punctured. A definite sensation is felt when the aortic wall is penetrated, analogous to that which accompanies penetration of the dura in a spinal puncture. When the stylet is withdrawn, there is a brisk flow of bright red blood which is not pulsatile unless the patient is hypertensive or the needle is located just above a block A second needle is inserted one-half inch proximal or distal to the first, parallel to it, and to the same depth. When the stylet of the second needle is withdrawn, a similar flow of blood occurs. We believe that the use of a second needle is a safeguard against insertion of one needle into a renal artery, the celiac axis, or the mesenteric artery. If a free flow of blood is not obtained with the second needle in the same position and at the same depth as the first, both needles are withdrawn and new punctures are made If doubt still remains, a test exposure with a small amount of opaque medium is obtained

"After the needles are placed in the correct position, Luer-Lok adapters connected to 8 to 10 inches of polyvinyl tubing are attached to each Two 10 cc Luer-Lok syringes, each overloaded with approximately 12 cc of the opaque medium, are attached to the tubing, again by means of Luer-Lok adapters. The syringes are clipped to a slide holder which allows more rapid injection than the former method of holding one syringe in each hand. The anesthetist then injects 5 cc of Pentothal Sixty seconds later the opaque medium is injected, the syringes being emptied as rapidly as possible. A total of 24 cc. of 70 per cent Urokon is used. The exposure is started just before the plungers reach the bottom of the barrel and continued after the injection is completed. We believe that this specified length of exposure



Fig. 51. Thrombotic obliteration of the aortic bifurcation—Leriche Syndrome (Translumbar Abdominal Aortogram). A 48-year-old male with intermittent claudication Film exposed following 2 to 3-second injection of 20 cc of 70 per cent Diodrast through an 18 gauge needle inserted via translumbar route Obstruction and collateral channels are outlined as are the renal arteries (Courtesy of Dr. Israel Steinberg and *Circulation*)

The technic of aortography used by De Wolfe and the Cleveland Clinic group (5) is given in detail *

"If the aorta is completely blocked in its terminal portion, a small amount of an opaque medium inserted through a single needle provides sufficient

* Courtesy of Dr. De Wolfe and by permission of *Circulation* (9 1, 1954)

Thrombo-endarterectomy (24-26) is a method of removing the obstruction in the aorta. The aorta is clamped above and below the site of obstruction. The intima, a portion of the media and the thrombus, if present, can be separated with surprising ease and removed through one or more incisions in the wall of the aorta This may weaken the wall considerably. Wylie (27) advocated wrapping of the aorta at this site with fascia to give additional support.

ARTERIOSCLEROTIC ANEURYSMS

Arteriosclerotic aneurysms occur predominantly in the terminal aorta, almost always below the renal arteries, and are usually fusiform dilatations in older individuals They rarely produce erosion of bone, and associated pain is apt to be mild and poorly defined Estes (28) reported that of 102 patients with abdominal aneurysm, almost all of which were due to arteriosclerosis, 67 per cent survived 1 year and 10 per cent for 8 years As for the average life expectancy of the normal population aged 65, 67 per cent will live for 8 years Only 27 5 per cent of the 102 patients with aneurysms were less than 60 years old at the time of diagnosis and only 6 9 per cent were less than 50 years of age The most common symptoms were abdominal pain and abdominal mass, but nearly a third of the patients had no symptoms. The most common physical signs were the presence of an expansile, pulsatile abdominal mass and a thrill or bruit. Roentgenograms disclosed scattered calcification in the aneurysms or in the aorta in a little more than half of the cases Rupture occurred in 63 3 per cent of untreated arteriosclerotic aneurysms.

While some aneurysms may remain stationary or even asymptomatic, nearly all of them leak, rupture (29) or become thrombosed The slowly leaking abdominal aneurysms is a definite entity (30) It is not a dissecting aneurysm and creates massive organized, fibrotic masses giving suspicion of retroperitoneal tumors. Despite the risk in untreated patients, Kirklin and Waugh (49) state that "patients with advanced coronary disease, manifested by recent or repeated myocardial infarctions or by severe angina pectoris probably should be denied operation." Patients with less severe coronary artery disease should be operated upon (58).

Enselberg (53) reported his experience with 34 proven cases of abdominal aortic aneurysm In this group, correct clinical diagnosis (including x-ray diagnosis) was made in only 16 There were 29 males and 5 females; 1 patient was 22 years old, 9 were between 52 and 57, 14 between 60 and 69, 9 between 70 and 79, 1 patient was 86 years old. The diagnosis in 32 patients was arteriosclerosis, in 1 case, syphilis, and in 1, the etiology was considered congenital Of these 34 patients, 26 died and 19 were autopsies. Rupture of the aorta occurred in 14 cases, in 6 of which this diagnosis was

is extremely important. Unless the opaque medium is in the aorta at the level of the needle tips, it is impossible to know whether the empty area below the needles and above the top of the dye column represents a block, or merely a region through which all of the opaque medium has passed before the exposure was made.

"The patient lies on an ordinary operating table at standard height in a fully equipped operating room. A portable Bucky, holding a standard 14 x 17 film, is placed under his abdomen A 60 milliampere portable x-ray machine which provides a 32 inch tube-to-film distance is used. The average exposure is 0 5 second at 80 kilovolts

"Because it is occasionally necessary to obtain an additional aortogram, the needles are maintained in place until the film is developed, unless there are anesthesia difficulties It is sometimes desirable to repeat the procedure in the case of a terminal aortic block with only moderate collaterals, with tourniquets on both of the patient's legs, to show the collaterals more clearly."

The importance of preoperative angiograms in predicting the success or failure of a grafting procedure was stressed by Humphries, de Wolfe and LeFevre (57). Their more than two-year experience is based on 120 freeze-dried homografts (77, aortoiliac and 43, femoral). The age of the patient, the presence or absence of diabetes or heart disease had little predictive value The importance of angiography was related not only to the determination of the length of the occluded segment but more specifically to the presence of patent distal vessels that were relatively free of disease and were capable of carrying the increased blood flow imposed on them by the graft When the preoperative angiographic findings were favorable, a 96 per cent chance existed that the graft initially would be successful Furthermore, if the occlusion was aortic, there was approximately a 95 per cent chance that the graft would remain satisfactory, if femoral, this became a 90 per cent chance. When angiography revealed an unsatisfactory outflow, the chances of a successful graft fell to 24 per cent.

Treatment: The treatment of thromboarteriosclerosis of the abdominal aorta is surgical. The following procedures have been recommended (4) (1) bilateral lumbar sympathectomy, (2) resection of the diseased portion of the aorta, with no graft, (3) resection of the diseased portion of aorta and repair with a graft, and (4) thrombo-endarterectomy Resection of the diseased portion of the aorta with replacement by a graft is the most commonly advocated procedure (14-19). The replacement graft may be a homologous aortic graft (20), a freeze-dried arterial hemograft (21), Vinyon "N" cloth (17), orlon cloth (18), or vena cava autografts with a buttressing support (52). Technics are given in the standard texts and in the papers on this subject (15-19, 22, 23, 48, 54, 55).

only in those with medium-sized or large lesions Resection of the aneurysm should be advised in all patients unless fresh coronary occlusion, cardiac decompensation or some other serious medical consideration makes the patient a very poor surgical risk.

De Takats and Pirani (31) believe that the pathogenesis of arteriosclerotic aneurysms is as follows:

"It is our feeling based on the reports of numerous investigators, that the 'local' factors, such as deposits of fibrin and other hemotogenous substances in the intima, accumulation of ground substance, and disruption of elastic lamellae in the media, but especially disturbances of circulation in the vasovasorum either on a functional or anatomic basis or both, play the initial and perhaps predominant role in this disease Of course, atheroma formation may further weaken the arterial wall and atheromatous ulcers in particular may in some cases be the basis of aneurysms formation. Foci of fibrosis and scarring of the arterial wall with or without lipid deposition, will result in the formation of inelastic and noncontracting areas

"Once the initial dilatation of the arterial wall has taken place, the course of the disease is progressive. Formation of mural thrombi within the aneurysmal cavity and extensive fibrosis of the arterial wall and of the periarterial tissues may delay expansion and rupture of the aneurysmal sac, but cannot prevent the inexorable progress of the lesion. At this stage three factors appear to be involved in determining the progress of the disease the level of the systolic blood pressure, the direction and force of the secondary blood currents within the aneurysmal sac, and the state of vascularization of the aneurysmal wall"

Treatment: 1. Excision of the Aneurysmal Mass with Its Feeding Vessels (17, 31-35, 51). In arteriosclerotic saccular or fusiform aneurysms, excision and replacement by autogenous vein or homologous arterial grafts is indeed a great advance in the treatment of this disease While autogenous veins will suffice in peripheral aneurysms, so far only arterial grafts have been used for replacement of segments of aorta On occasion, the spleen has been removed and the splenic artery has been anastomosed to the iliac artery (36)

De Bakey *et al.* (19) have reported resection on 76 abdominal aortic aneurysms Of a total of 89 thoracic and abdominal aortic aneurysms combined, there were 20 deaths and an operative mortality of 22 per cent.

2 Wiring, wrapping with cellophane, partial constriction and their combination (32), painting or spraying with 1 per cent dicetyl phosphate, surrounding the bulging sac with steel mesh, or Ivalon sponge (50).

Blakemore and Voorhes (35) report that from January 1932 to June 1953 the diagnosis of aortic aneurysm was made in 365 cases. Of these, 143 were arteriosclerotic (29 thoracic and 114 abdominal). Two hundred eleven of the total series were surgically treated as follows. wiring and thermo-coagu-

missed. No patient survived rupture and only 3 could be subjected to reparative surgery. The most common symptoms associated with abdominal aortic aneurysm were lower backache (usually on the left side), low abdominal pain and pain simulating renal colic. Referral along the posterior thigh occurred in a few. Only 5 patients had no symptoms explainable on the basis of aneurysm.

A palpable abdominal mass was found in 21 cases. In 16, the mass exhibited expansile pulsations, and in 15 it was tender. Murmurs and thrills were noted in 5 and 4 cases, respectively In only one instance was it specifically noted that the mass was not tender X-ray examination revealed calcified outlines of the aneurysmal wall in 12 cases. In 7 instances aortography was diagnostic. In 4 cases indirect signs were found, such as a soft tissue mass or displacement of the kidney and ureter were noted on pyelography. The 14 patients with rupture all presented the classic picture of hemorrhagic shock. In almost every case a history was obtained which pointed to retroperitoneal involvement (severe backache, "renal colic"). Reflex ileus was common in patients surviving 2 days. However, 9 of the 14 died within 48 hours. In 4 cases it seemed probable that small extravasations had occurred weeks or possibly months before the major catastrophe Rupture was usually through the posterolateral aspect of the aorta into the retroperitoneal space. Intraperitoneal hemorrhage was found only twice In 2 cases, rupture occurred in associated thoracic aneurysm whose presence was unsuspected.

Crane (56) reviewed the autopsy protocols and the clinical records of 44 patients with abdominal arteriosclerotic aneurysms. The series consisted of 37 men and 7 women; the age range was 39 to 93 years with two-thirds in their sixth or seventh decade. Twenty-four patients were hypertensive (160 mm. of mercury, systolic, or 90 mm. of mercury, diastolic, or more). In 42 cases in which the coronary arteries were examined, they were said to be normal in only one. Six cases had old coronary occlusion, 10 fresh and 4 showed both Recent coronary-artery closure was thought to be the chief cause of death in 14, or about a third of the cases Arteriosclerosis of the generalized type (peripheral arteries, visceral arteries, heart and brain) were found pathologically in 41 patients. When the aneurysms were classified according to size, it was found that 82 per cent (14 of 17) of those 7 cm. or more in diameter had ruptured while only 1 of 26 or 4 per cent of those less than 6 cm. in diameter ruptured. Only 3 of the 44 aneurysms lay above the renal arteries. The great majority of the 15 patients with ruptured aneurysms had had symptoms for only a short time before entry into the hospital. Three of the 15 patients died within less than 6 hours of hospital admission, 5 lived for 12 to 24 hours, and 7, for 1 to 6 days The recommendation is made that asymptomatic patients with arteriosclerotic abdominal aneurysms should be studied with special attention to cardiac function, coronary artery disease and renal function. Aortography should be done

acterized by the sudden occurrence of agonizing abdominal pain, usually accompanied by nausea and vomiting Exquisite tenderness and board-like rigidity of the abdominal wall rapidly develop. The blood pressure and frequently the body temperature falls Abdominal distention with constipation becomes marked. If bowel movements occur, the stools are usually bloody. In the absence of melena, the clinical picture strongly suggests intestinal perforation. Gangrene of the infarcted segment of bowel, peritonitis, and death rapidly ensue, unless the affected portion of the gut can be resected or splanchnic block (41) can restore some mesenteric circulation.

Morris (43) and Seymour and Liebow (47) indicated that as the progressive narrowing of the mesenteric arteries occur, the patient may complain of "intermittent intestinal claudication" or "abdominal angina" This, Morris (43) states, may represent itself as an aching, gnawing, abdominal pain coming on one or two hours after meals Finally the thrombosis occurs giving rise to the clinical picture described above.

Larger aneurysms (45) may be detected by physical examination, by auscultation of a bruit and by the presence of calcification in the aneurysmal sac on roentgenography.

INNOMINATE ARTERY THROMBOSIS

Thrombosis of this artery due to arteriosclerosis is extremely rare Zondek (46) reports the history of such a patient in whom an atheromatous innominate artery with thrombus formation was found at pathologic examination The author felt that the thrombus formation was due to infection although no cause of such infection could be found in the clinical history or in any of the laboratory investigations The thrombus extended into the right common and internal carotid arteries and there was intensive softening of the right cerebral hemisphere

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lation, 101, wiring alone, 25, banding, 7; banding, wiring and thermocoagulation, 52, wrapping, 14; ligation, 4; grafting (excision and graft), 4, resection (neck or saccular), 4.

The electro-thermic method is employed as follows (35):

1. At a first stage operation, the object is to clot the fusiform aneurysm to the point of decreasing considerably the blood flow through the aorta via the aneurysm as a stimulus to the development of adequate collateral circulation This is to be attained by the introduction and heating of ten meter segments of insulated wire

2. At a second stage, complete closure of the aorta is attained by the introduction and heating of additional segments of insulated wire.

3. Since from experience, it is known that to eliminate the threat of rupture and achieve permanent inactivation (cure) of the aneurysm requires exclusion of aortic blood flow at the aneurysm site, it is necessary on many occasions to do a third operation involving wiring. The technic is as follows

The wiring operation is performed in two stages with a 3-week interval in between. At the first operation several 10-meter segments of fine insulated coin silver wire are distributed throughout the aneurysm Each segment of wire is heated to an average temperature of 80 degrees C for a 10-second period At the second operation several segments of wire are concentrated in the lower half of the aneurysm. Heating of these final segments of wire results in complete occlusion of that portion of the aneurysm distal to the renal arteries.

In 1948, the method of banding was devised by Blakemore. The method entails the employment of a wide (1.5 cm) heavy, rubber band, which prior to its introduction is encased in some 16 to 20 layers of polythene dicetyl-phosphate, plastic film On tightening the band upon the aorta, the intervening plastic film is in pressure contact with the aorta. The presence of the irritant dicetyl-phosphate, stimulates fibroplasia and has proved efficient in the prevention of necrosis of the aorta wall with secondary hemorrhage. De Bakey and his group (37) found that in 8 cases of abdominal aortic aneurysm treated by polyethylene wrapping and subsequently resected (7 to 41 month interval) that although symptomatic improvement occurred in some patients following the polyethylene wrapping procedure, there was eventual recurrence of symptoms and progressive increase in size of the aneurysms in all the patients. With Ivalon sponge, Grindlay *et al.* (50) found that 33 3 per cent of patients so treated died from aortic rupture in from 6 months to 2 years

MESENTERIC THROMBOSIS (38-43)

The syndrome which develops with occlusive lesions in the mesenteric arteries resulting in infarction of the bowel, is by far the most definite clinical expression of arteriosclerosis of the abdominal vessels. This is char-

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Chapter XI

Peripheral Vascular Aspects of Arteriosclerosis

BLOOD SUPPLY

THE SUBCLAVIAN artery (Fig. 52) arises on the right from the innominate artery and on the left from the aortic arch It terminates at the outer border of the first rib as the axillary artery. The axillary becomes *the brachial artery at the lower border of the teres major and this divides* into the radial and ulnar arteries just below the head of the elbow

The femoral artery (Plate IX) is a continuation of the external iliac artery and it proceeds down the anterior and medial side of the thigh into the popliteal space where it becomes the popliteal artery (Plate X) The *anterior and posterior tibial arteries are branches of the popliteal* The anterior tibial at the first interosseous space where it divides into the first dorsal metatarsal artery and the deep plantar The posterior tibial artery becomes superficial at the medial aspect of the leg below the internal malleolus an important fact in its physical palpation. The peroneal artery arises from the posterior tibial artery and divides near the fibula into lateral calcaneal branches.

TYPES OF PERIPHERAL ARTERIOSCLEROTIC DISEASE

1. Monckeberg's Arteriosclerosis
2. Arteriosclerosis Obliterans.

MÖNCKEBERG'S ARTERIOSCLEROSIS

Monckeberg's arteriosclerosis (1) is a clinically benign form of calcifica*tion of the* blood vessels. The clinical characteristics that distinguished Monckeberg's sclerosis from other forms of arteriosclerosis are extreme calcification of the arteries of the lower extremities in young and middle-aged persons who have no symptoms or signs of impaired circulation. Silbert *et al.* (2, 3) found only 53 cases during the same period that over 3,500 cases of arteriosclerosis obliterans were observed In 6 of their cases, Monckeberg's arteriosclerosis was associated with occlusive arterial disease (4, coronary; 1, peripheral, coronary and cerebral).

Pathologically, Monckeberg's sclerosis is characterized by a deposit of calcium in the media of the arteries There is no thickening of the intimal layer, which is the most striking feature in true arteriosclerosis, and the



Plate IX. The femoral artery. (From *Gray's Anatomy*, 26th Ed. 1954. Courtesy Lea & Febiger, Philadelphia.)

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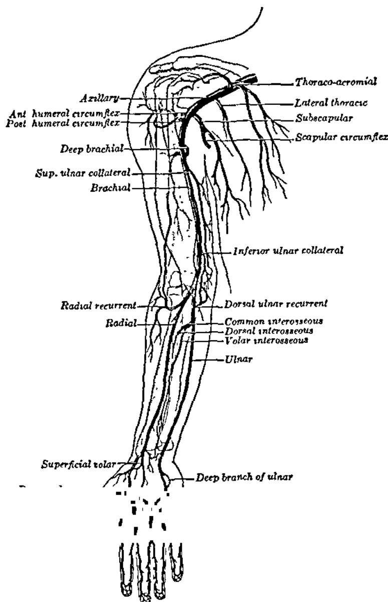


Fig 52 The arteries of the upper extremity (From *Gray's Anatomy*, 26th Ed., 1954. Courtesy Lea & Febiger, Philadelphia)

blood vessel lumen is therefore not narrowed The surface of the intima remains uninjured and thrombosis does not occur

The clinical features point up the complete absence of any symptoms or signs of impaired circulation in the extremities All pulsations are easily felt and are normal in size. Oscillometric and temperature studies indicate a normal blood flow. Males alone seem to have this disease. No treatment

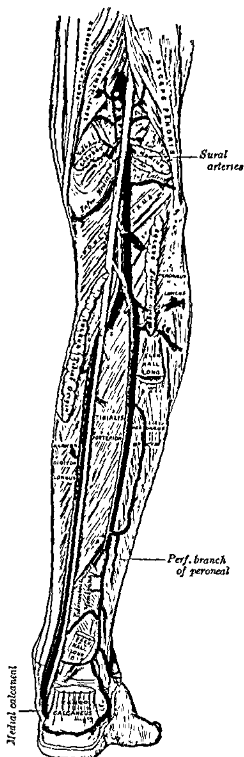


Plate X The popliteal, posterior tibial and peroneal arteries. (From *Gray's Anatomy* 26th Ed., 1954. Courtesy Lea & Febiger, Philadelphia.)

and on the site of ischemia. Reducing the rate of walking or shortening the length of the step (6) may delay or prevent claudication

2. Rest Pain. As arterial insufficiency progresses, a point is reached where pain is present at rest. It is more commonly noted at night, especially after the patient had gone to sleep. Such patients may spend sleepless hours rubbing the painful foot. Occasionally, placing the extremity in a dependent position relieves the pain Such pain may be indicative of a sudden arterial occlusion or be part of a gradually progressive chronic arterial occlusion.

Constant pain at rest may also occur with ulceration and gangrene which represents a further step in circulatory insufficiency. These pains are to be contrasted with the pain of ischemic neuritis which usually occurs over large portions of the skin and may follow the distribution of the peripheral nerve trunks The pain is of burning character. It occurs more commonly among diabetic patients

Paresthesias, such as numbness, deadness, prickling, tingling may occur secondary to arteriosclerosis obliterans and ischemic neuritis. A degree of cold sensitivity may develop even in the early stages. Muscular weakness may be seen with extreme degrees of arterial insufficiency

Physical Examination: Pulsations in the posterior tibial, popliteal and femoral arteries, when absent in a patient at rest and in a warm environment, indicate occlusive arterial disease. The dorsalis pedis artery is absent, normally in as high as 12 per cent (73) of the population due to an anomalous distribution in the deeper tissue. Examination of the extremities in the horizontal, dependent and elevated positions will bring out such cardinal color changes as rubor on dependency and pallor on elevation. A difference in the temperature on palpation between the two feet or legs is much more significant than equal coldness of both feet.

The digits should be inspected for scarring, shrinkage, impairment of nail growth and lack of hair growth (7) Ulcers, gangrene and infection should be noted The more severe degrees of chronic arteriosclerosis obliterans give rise to atrophy of the muscles, skin and osteoporosis of bone Edema may be due to local arterial insufficiency but its occurrence as part of congestive heart failure should be investigated

Laboratory Examination: The following are helpful.

1 Roentgenograms of extremities for calcification

2 Skin temperature studies before and after posterior tibial nerve block or elevation of temperature in another way to give definite information as to degree of vasospasm and degree of organic arterial occlusion (9)

3 Oscillometry Atlas (8) compared the oscillometric reading at the ankle with that at the wrist and expressed the result in the form of a ratio. Since arteriosclerotic changes usually progress more rapidly in the lower

of any kind is necessary. Nocturnal leg cramps can be relieved by oral calcium lactate.

Roentgenographically, typical cases show dense uniform calcification which outlines the major arteries and their branches. The calcium appears to be deposited in transverse lines giving the appearance of a chain of rings similar to a goose neck. In contrast, calcification in intimal arteriosclerosis is patchy, dispersed, and tends to be deposited in the long axis of the blood vessels

ARTERIOSCLEROSIS OBLITERANS

Arteriosclerosis obliterans is a type of arteriosclerosis occurring typically in the lower extremities which results in episodal occlusion of the arterial lumen (5).

Pareira *et al* (4) studied the major arteries and veins of 45 lower extremities Thirty-six of the 45 limbs had been amputated because of gangrene resulting from vascular occlusion on an arteriosclerotic basis They concluded that the aging process in arteries starts at an earlier time than was previously appreciated. For example, the popliteal artery in a patient aged 20 years already may show significant changes. The aging process may be summarized as follows First there is intimal thickening due to collagen with an increase in the elastic fibers of the intimal elastic lamella and early deposits of calcium along the elastic fibers, later the elastic filaments increase in the intima and media and calcification about them increases, the calcification increases with rock or bone formation, atheromatous plaques appear late in the process and occurs in the muscular wall as well as the elastic arteries. It would appear that the hydrostatic tension in the vessel is an important factor in determining the rapidity of this aging process since its localization and rate correlate with high tension The incidence of thrombosis at given locations indicates a relation exists between the caliber of the vessel and the degree of atheromatous change

Incidence: It occurs predominantly among men (6 1 ratio with women) between ages of fifty to seventy years. In 280 cases reported by Allen, Barker and Hines (5), diabetes mellitus was found in 57 (20 3 per cent) Hypertension was found in ninety-nine cases (35 per cent) Eighteen additional patients had retinal arteriosclerosis

Symptoms: 1. INTERMITTENT CLAUDICATION The patient with arterial insufficiency usually first complains of symptoms of intermittent claudication (69). This is manifested by a sense of tightening of the muscles, or cramping and an inability to walk, with relief after cessation of walking and rest even though this be in the upright position. Symptoms are usually unilateral at first, may become bilateral at any time but at almost any stage of the disease is worse in one leg than the other The area of pain may be anywhere from the hip to the foot, depending on the site of intimal sclerosis

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reached after 0 68 minute During the vasoconstrictive phase the toe flow declined on the average to 4.1 cu. mm In arteriosclerosis obliterans, patients with tissue changes, the average blood flow was 1.9 cu mm. per 5 cc.

The plethysmograph may be used to measure the change in peripheral blood flow produced by emotions (13).

5. ARTERIOGRAPHY (5, 67-68c) is useful in determining alteration in caliber of lumina, the presence of complete occlusion and the presence or absence of collateral circulation, but it is considerably less important as a routine procedure in peripheral vascular disease than is aortography as a pre-operative diagnostic procedure for segmental resection

6. FLUORESCEIN (14-16) · An aqueous solution of sodium fluorescein when injected intravenously, will give a greenish yellow glow when observed under an ultraviolet light in a darkened room This method may be used for determining circulation time on the extremities of patients with peripheral arterial disease. Sicher (17) found circulation times in arteriosclerosis obliterans as long as 51 to 154 seconds The usual time to the foot is about 34 to 36 seconds. The test may also be used to indicate levels of arterial occlusion in instances where gangrene is present and the level of adequate circulation is desired.

7. RADIOACTIVE SODIUM. Mufson (18, 19) has described the use of radioactive sodium to test the effect of drugs in peripheral arterial insufficiency. The testing is done as follows The patient is supine and is allowed to remain recumbent for 15 minutes before the test is started The window of a Geiger counter is placed against the sole of the foot and under the calf alternately for 6 to 8 minutes at a time, while the count is taken every minute after the injection into the ante-cubital vein of about 100 microcuries of radiosodium in a sterile solution of physiologic saline The counter registers the local arrival of the radioactive material in the blood stream and the graphias plotted from these measurements represents its rate of accumulation in the extremity. A basic curve without drug is compared with the curve after drug To correlate the radiosodium studies with objective findings, skin temperatures and oscillometric readings are recorded during the test.

This method has confirmed the effectiveness of histamine and of sympathetic block as vasodilators in obliterative disease of the leg In the same patient, intra-arterial papaverine, aminophylline and intravenous Etamon was found to be ineffective where histamine intra-arterially was affective.

8 CALORIMETRY: Using his own calorimetric method for measuring digital blood flow, Mendlowitz (20, 21) found that decreased hallucal circulation was an early manifestation of vascular disease in diabetes mellitus. The hallucal circulation was measured after inhibition of sympathetic nerve discharge by approximately 1 hour of indirect heating, supplemented by the

than in the upper extremity, the reading at the wrist may be assumed to represent each patient's approximately normal value, and Atlas demonstrated that the oscillometric (ankle:wrist) index provided a better basis for evaluation of the arterial status in the leg than does an oscillometric reading at any single level of the extremity. In a series of 90 normal adults, he found this ratio to be 1 or more, whereas in a series of 100 persons with arteriosclerosis of the lower extremities, the ratio was found to be less than 1 For these patients with low oscillometric indices, the absolute oscillometric value proved misleading as a criterion of arterial disease of the extremities since in half of them, despite the absence of pulsation in both the dorsal pedal and the posterior tibial arteries, the oscillometric reading at the ankle was 1 or more, which is generally accepted as normal

Rinzler, Travell and Civin (9) determined the oscillometric index, the cutaneous temperature following posterior tibial nerve block and the presence or absence of calcification of the vessels of the lower extremities in roentgenogram for 84 ambulatory patients with heart disease. A correlation of the data obtained by these three laboratory aids shows that as the oscillometric index decreases, the incidence and extent of calcification of the vessels of the lower extremity and the incidence of abnormal cutaneous temperatures increase.

In the presence of a normal circulation in the upper extremity, an oscillometric index of 0.75 indicates sclerotic changes in the arteries of the leg, probably with calcification, and an index of 0.3 or less indicates extensive calcification and probably advanced occlusive arterial disease The oscillometric index is of greater value in estimating the presence and degree of arteriosclerotic disease in the lower extremity than in the oscillometric reading at the foot or ankle when the latter readings fall within an intermediate range of about 1 to 4 at the ankle and 1/8 to 2 at the foot. An oscillometric reading of more than 4 at the ankle or more than 2 at the foot nearly always indicates normal arterial flow, and a reading of less than 1 at the ankle or 0 at the foot indicates occlusive disease.

4. Plethysmography The plethysmograph (10, 78) measures changes in volume per unit time Variations in such volume has been used as early indications of the onset of peripheral vascular sclerosis (11, 12). Megibow *et al.* (12) found that the characteristic pulse wave alterations and the increased pulse volume which normally follow the administration of nitroglycerin are absent or are minimal in the presence of organic vascular disease.

Winsor (11) studied the reactive hyperemia following 15 minute arterial occlusion at the ankle by means of plethysmographic tracings. The normal subjects had a mean resting blood flow of 7.8 cu. mm per 5 cc per second, the maximum toe flow amounted on the average to 20.8 cu. mm., and was

parenterally. The use of vasodilating agents and the route of administration is usually determined by the clinical condition.

Locally, it is best to expose the foot to the air without dressings and to keep the patient in bed with his foot level if there is no cellulitis or lymphangitis (in which case the foot is slightly elevated). A cradle is used to protect the foot. Wet dressings are used in the presence of cellulitis or lymphangitis. For the lesion itself, antibiotics should be used locally. Many prefer an antibiotic powder so as to keep the lesion dry since it is believed that antibiotics in ointment form may macerate the tissues. This must be considered in using tryptar or streptokinase ointments It is wise to rule out osteomyelitis.

Where the lesion is progressive or where rest pain becomes a problem, one must consider inter-arterial histamine or priscoline or paravertebral block The latter is usually accomplished with a polyethylene catheter in place so that procaine may be instilled several times daily over a period of several days.

TRYPSIN Innerfield, Angrist and Schwartz (55) found that intravenous administration of trypsin consistently produced fibrinolysis in dog and rabbit experiments and extended these observations to the problem of the fibrin network of human intravascular thrombi. The material was administered as follows· under sterile conditions a vial containing 10 mg of trypsin was dissolved in 3 cc. of isotonic sodium chloride, and 1 cc (10 mg) of methapyrilene hydrochloride (histadyl) was introduced into the flask. The intravenous injection was started immediately Each dose consisted of 10 to 15 mg of trypsin dissolved in 100 cc of isotonic sodium chloride solution. A typical course of therapy consisted of 10 mg of trypsin per infusion, twice daily, for 5 to 7 consecutive days.

Fisher and Wilensky (56) treated 42 patients with peripheral arteriosclerosis with and without gangrene of the heel or the toes with repeated intravenous infusions of trypsin in ascending doses of from 10,000 to 50,000 Armour units with little or no effect on the course of the disease Twenty of the group had diabetes and with those who had infected lesions of the toes, as paronychia, the infection seemed to subside more promptly with than without it. No improvement was noted in the peripheral circulation in the diabetic arteriosclerosis Intramuscular trypsin in a concentration of 5 mg. per cc in sesame oil was tried in 2 patients with peripheral arteriosclerosis obliterans with no effect on the course of the disease.

Thrombosis at the site of the intravenous infusion has been encountered (57, 58). Taylor, Overman and Wright felt that there was insufficient evidence to justify the use of trypsin for the therapeutic purposes in man (57).

Tryptar has been used for the enzymatic debridement of indolent infected

intravenous injection of tetraethylammonium chloride in dosage of 5 mg. per kg. of body weight.

9. TWO-STEP TEST IN INTERMITTENT CLAUDICATION: Kissin, Stein and Adleman (22) described a two-step test of exercise tolerance which they found to be a satisfactory and convenient measure of exercise tolerance in intermittent claudication. The patient walks back and forth over the steps until pain appears in the legs. The exercise tolerance test when done repeatedly on a single day was found to be constant, as was day to day measurements, a factor useful in the chronic experiments on intermittent claudication and in following progression or regression of symptoms.

TREATMENT OF ARTERIOSCLEROSIS OBLITERANS

Foot Care: The patient should be given the following instructions: Do not wear shoes that are too tight. Wear white cotton socks in warm weather, woolen socks in cold weather and change socks daily. Be careful of any wound. Do not use iodine if you scratch or cut your foot. Wash the wound with soap and water and cover it with a piece of sterile gauze until your doctor sees it. Do not cut your own nails, corns or callouses Some responsible member in the family or a podiatrist should attend to this. Do not use hot water bags, electric pads or baking lamps without asking the advise of your doctor

Diet: The relation of diet to arteriosclerosis has been covered in Chapter I. The only specific recommendation is reduction in weight in obese patients

Tobacco: Although there is no etiologic relation between smoking and arteriosclerosis obliterans (82), the use of tobacco causes arteriolar constriction (5, 81) and *patients should be advised to refrain completely.* It has been found by Weinroth and Herzstein (83) that in a group of male patients with diabetes mellitus, that the incidence of arteriosclerosis obliterans in smokers was more than twice that in non-smokers.

The Treatment of Ulcers of the Toes in the Presence of Arteriosclerosis Obliterans Alone or Complicated by Diabetes: During the course of arteriosclerosis obliterans, patients may develop spontaneous thrombosis of the arteries of the leg which may lead to gangrene of one or more digits or to traumatic or nontraumatic ulcers. The usual history is that the patient with diabetes gets pressure put upon the toes by a shoe, develops a blister which goes on to ulceration Because of the possible complication of peripheral neuropathy, pin-prick and sensation may be diminished or absent, thus adding to the possibilities of pedal trauma

The general therapeutic measures include control of diabetes by diet and insulin, administration of antibiotics, vitamin B_{12} in doses of 1000 mcg. 3 times weekly intramuscularly and thiamine chloride 100 mg daily, also

parenterally. The use of vasodilating agents and the route of administration is usually determined by the clinical condition

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Tryptar has been used for the enzymatic debridement of indolent infected

cutaneous ulcer (59). This is prepared by dissolving 250 mg. of purified crystilline trypsin solution in 25 cc. of Sorensen's reagent.

VARIDASE: Varidase Streptokinase-Streptodornase is available in 2 packages which has the enzymes in the following amounts: Streptokinase 100,000 units and Streptodornase at least 25,000 units, or Streptokinase 20,000 units and Streptodornase at least 5,000 units.

For the topical use of Varidase, Carboxymethylcellulose Jelly is available. One jar of the jelly is mixed with one vial of Varidase after the latter is reconstituted with 5 ml. of sterile distilled water. The resulting mixture will contain approximately 5,000 units of streptokinase and 1,250 units of streptodornase per gram. This mixture is stable for 7 days. The jelly mixture can be kept in situ by means of gauze or plastic bandages.

Indolent ulcers may be treated by local application of Varidase alone or the varidase jelly.

McVay and Sprunt (60) treated 5 diabetic patients with gangrene with streptokinase and sterptodornase. In 4 instances aureomycin was alone applied locally. Excellent results were noted in 3 cases, and definite improvement in 2. There was evidence of recurrence of gangrene. For example, 1 patient with a painful ulcer of 2 months duration, located between the third and fourth toes, was treated by placing on the ulcer a small pledget *soaked in 3 ml. of solution of 180,000 units of water. Within 24 hours, there* was no evidence of purulent material The same procedure was carried out daily for one week. Forty-eight hours after the institution of therapy, the wet necrosis had been replaced by dry gangrene Lesser or greater concentrations of the material were used in the other cases

Gilfillan *et al.* (79) studied the filling pressure of the minute vessels of the skin of the foot by a method of elevation and reactive hyperemia and then used this knowledge to treat and prognosticate necrotic lesions of the foot

Drug Therapy: The drugs used may be divided into four groups: (1) *adrenergic blocking agents such as, Ilidar, Dibenzyline, and Dibenamine,* (2) ganglion blocking agents such as, Hexamethonium and Tetraethylammonium chloride; (3) central acting drugs such as, Hydergine and (4) drugs with a direct action on blood vessels such as histamine.

Where intermittent claudication and coronary artery disease co-exist in [illegible] whether or not the administration [illegible] ts, such as dibenzyline, may not [illegible] further complicated in a patient where both intermittent claudication and effort angina are active symptoms In such instances, one may turn to drugs which have a dilator effect both on the coronary arteries and on the peripheral vessels such as nitroglycerin or hydergine.

1. PRISCOLINE (23-29): Priscoline (2-benzyl 1-4, 5- imidazoline hydrochloride) exerts its adrenergic blocking effect in the periphery. In addition to blocking responses produced by stiumlation of the sympathetic nerves or injection of epinephrine, Priscoline appears to have some direct local action due to its dilating effect on the vessel wall. The drug is neither necrotizing to tissue nor is it irritating to the vascular endothelium.

Dosages: Oral—25 to 50 mg. four times a day.

Intra-arterial, intramuscular or intravenous—25 to 75 mg.

Ion transfer—10 per cent concentration both in aqueous and ointment form (27).

Side-Actions (1) Tightness of scalp (2) Goose flesh and chilliness. (3) Nausea and/or vomiting. (4) Listlessness and/or irritability. (5) Palpitations (6) Increased sweating. (7) Increase in precordial pain (24)

Comments. In instances when acute arterial occlusion has occurred or when gangrene or rest pain has eventuated, or when oral doses are ineffectul, the intra-arterial injection may be indicated. This method has been found safe (28, 30, 31) and because even in the presence of advanced arterial disease, an injection does not irritate the injected arteries or periarterial tissues Because of the special nature of the technique, and the aseptic precautions necessary, it should be carried out only by the experienced and preferably, in the hospital or clinic The injection sites most frequently used are (1) the femoral artery immediately below Poupart's ligament; (2) the brachial artery at the superior angle of the antecubital fossa just medial to the biceps tendon, (3) the radial artery at the usual site for pulse-taking and (4) the external carotid artery just above the level of the thyroid cartilage in the anterior triangle of the neck, with the head turned to the opposite side.

The patient is supine and should be kept so for one-half hour after the injection A skin wheal is raised by procaine injection at the appropriate site Through this wheal a 22-gauge needle is inserted at right angles into the artery. The color of the blood will indicate the entrance into the artery and the intra-arterial injection should be made slowly over a period of three or more minutes. Injections may be repeated daily as necessary The use of an intra-arterial catheter (polyethylene plastic) and an apparatus for constant infusion may facilitate this The patient may be ambulatory when the infusion is not in progress, the intra-arterial catheter being left in place.

2. HISTAMINE. Intra-arterial histamine (18, 32, 33) in repeated infusion has been stated to increase the blood flow through the arteries and thereby to cause a structural increase in the diameter of the lumen. When this forced increase in blood flow follows the arterial introduction of a vasodilator, the collateral arteries will become larger and more numerous Mufson (32) lists the following reasons for choosing histamine

a) It caused the most intense and extensive erythema.
b) It is safest because it is a natural body constituent.
c) It may be used in coronary but not in asthmatic patients

Dosage. Histamine acid phosphate 2.75 mg. in 1 cc or 5 cc. The dose is 1 mg. to 2 75 mg. in 300 to 500 cc. of sodium chloride solution once or twice weekly for walking, two to three times weekly for night pain, or daily for infection and acute ischemic neuritis. The time for infusion is one-half hour.

Comment: The intra-arterial administration of histamine must be given under pressure as an arterial infusion. Antibiotics may be added to the infusion. During an arterial infusion (33), the following changes may occur. Increase in heart rate, stroke volume, cardiac output, skin temperature, oxygen saturation in the femoral vein, decrease in the blood pressure and oxygen saturation in the injected artery and arteriovenous difference

A minimum of 10 arterial histamine infusions will increase the walking distance to 7 or more blocks in 52 per cent of cases (32) and in those with no popliteal pulse will relieve horizontal rest pain. Dixon and his co-workers (33) state that "intra-arterial histamine may have a limited field of therapeutic usefulness in selected cases of occlusive arterial disease in a class of patient that has been regarded as refractory to treatment."

3 PAPAVERINE and its derivatives are described in Chapter IV. The doses and routes of administration are similar for peripheral vascular disease as for angina pectoris.

4. ERGOT ALKALOIDS. Hydergine is a combination of three hydrogenated alkaloids (dihydroergocornine, dihydroergocristine, and dihydroergokryptine) It has a peripheral sympatholytic action and a central action through the vasomotor center resulting in a decrease in vascular tone (34).

Dosage. 0.5 mg to 2 mg administered orally or sublingually three to four times per day. One cc. administered intramuscularly from daily to two to three times weekly (88).

Comment· Roberts, Anderson and Parry (34) report on a total series of 35 cases (26 male and 9 females) with arteriosclerotic peripheral vascular disease, 12 of whom had intermittent claudication. Four improved on hydergine Six patients had ulcerative lesions and all healed, 4 within 6 weeks, 1 within 8 weeks, and 1 required 6 months

5 TETRAETHYLAMMONIUM CHLORIDE: This drug produces an autonomic blockage with resultant peripheral vasodilator action.

Dosage: Intravenous dosage is 100 to 500 mg. at the rate of 200 mg. per minute. Intramuscular dosage is 20 mg per kilogram, but not to exceed 1 to 1.2 gm, half being injected into each buttock

Actions. Fisher (35) described the effects of intravenous administration. After the injection, a metallic taste on the tongue is usually described Then

a flushing and feeling of warmth, accompanied with a sensation of pins and needles comes over first the upper then the lower extremities. An incomplete dilatation of the pupil occurs, accompanied by temporary blurring of the vision and a sluggish reaction to light. Usually, there is an elevation of the heart rate to about 120 beats per minute. The mouth becomes dry. There is a rise in the skin temperature of the fingers and toes. The blood pressure remains depressed for several minutes. Usually the diastolic pressure is the first to start to rise. Sometimes the injections cause weakness, sleepiness, dyspnea, light-headedness, difficulty in performing voluntary movements and in urinating. The contraindications in cardiacs have been given in Chapter IV. Prostigmine, in dosage of 1 to 2 cc of 1:2000 solution is the antidote for tetraethylammonium.

Comment· Fisher (35) found relief of rest pain in patients with gangrene and arteriosclerosis obliterans

6 HEXAMETHONIUM: This is an autonomic ganglion blocking agent. It is given intravenously in doses of 50 mg. It is approximately as effective (36) as paravertebral sympathetic block. The advantages lie in its ease of administration and extreme potency, permitting more or less continuous inhibition of neurogenic vasospasm for long periods. Its disadvantages are the development of hypotension and constipation.

7. DIBENAMINE AND DIBENZYLINE: Dibenamine is a synthetic nitrogen mustard which can be given only intravenously. The dose is 5 to 10 mg. per kilogram in 500 cc. of saline in 1 hour It may cause severe nausea and vomiting, visual impairment, postural hypotension, loss of bladder control, restlessness and mental confusion Dibenamine relaxes vessels by blocking the excitatory but not the inhibitory responses to sympathetic stimulation

Dibenzyline (SKF 688 A) is a specific sympathetic blocking agent (37) with an action similar to dibenamine but with greater potency and less toxicity. Dibenzyline may be given orally Dibenzyline effects its blockade at the neuroeffector junctions similar to Priscoline Pressor effects from circulation adrenergic substances (i.e, epinephrine) are blocked as are stimuli from sympathetic nervous system impulses.

Dibenzyline may be given orally in daily doses of 60 to 200 mg *in single* or divided doses, intravenously in doses of 0.7 to 1 0 mg per kilogram is a 200 cc. infusion in a 35 to 40-minute period, or intra-arterially in doses of 35 to 80 mg. in a 3 to 4-minute period Side reactions include: Nasal congestion; sweating, postural hypotension, and tachycardia A "quinidine-like" effect of the drug on heart muscle may occur and should be noted when the drug is given to patients with heart disease.

Oral dibenzyline (28) is a more potent agent than Priscoline in "vasospastic" states but only occasionally is it superior to Priscoline in arteriosclerosis obliterans. Moser and his co-workers feel (28) that use of Priscoline and

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Actions: Fisher (35) described the effects of intravenous administration. After the injection, a metallic taste on the tongue is usually described Then

arteriosclerosis obliterans are given by Pearl and Rosenman (42). If the arterial insufficiency progresses under treatment, sympathectomy should be done in any stage unless the patient is an obvious candidate for amputation. If the symptoms and signs of arterial insufficiency remain unchanged over a three months period of conservative management, operation is indicated. Extremities with mild degrees of arterial insufficiency and with one foot pulse present may be treated conservatively over extended periods, so long as the insufficiency does not progress The extremity deprived of part of its normal blood supply may hold its own under ordinary conditions, but comparatively mild insults, bacterial, chemical, mechanical or thermal, are prone to precipitate ulceration or gangrene and threaten the integrity of the limb. Sympathectomy should be advised when the threat is apparent and when the operation gives good promise of alleviating or removing it (70) Procaine block as a preoperative test for the effect of sympathectomy on rest pain or claudication has not proved dependable in their hands.

Edwards and Crane (43) analyzed the results of 100 patients with symptomatic arteriosclerosis of the lower extremities who were subjected to lumbar sympathectomy. Twenty-seven were diabetics. There were 2 hospital deaths and 6 early thigh amputations Ninety-two patients left the hospital improved. The patients were followed for varying periods up to 3 years, and a few up to 9 (average follow-up was twenty months). In this time 9 more patients died. The living 89 patients showed that the sympathectomized foot after unilateral operation was almost invariably better than its unoperated fellow. Patients with necrosis down to bone proximal to the toes did so badly as to suggest that this finding constitutes the only definite contraindication to the operation. Unfavorable factors included the presence of diabetes, other visceral disease, extreme hypertension and the previous loss of the contralateral limb. No correlation could be made between the following factors and the outcome Age; sex, the level of blood pressure between low limits and moderate hypertension, level of occlusion of the major arteries, or the degree of calcification of the arteries apparent in the x-ray film

De Bakey, Creech, and Woodhall (44) considered sympathectomy the method of choice in the treatment of arteriosclerotic peripheral vascular disease unless there exist definite contraindications to operation, such as severe cardiac, cerebral, renal or pulmonary involvement, a far advanced and rapidly progressive process, and pronounced atrophic changes in the extremity. They also found sympathetic block as a preliminary procedure to test the value of sympathectomy not an entirely dependable test. Their series comprised 146 patients, 55 of whom had bilateral involvement. All patients were followed for at least 6 months, three-fourths for more than 1 year, and 38 per cent from 2 to 4 or more years. The best results were

dibenzyline in the older group with arteriosclerosis should be used with extreme care. In nine of ten arteriosclerotic patients who received dibenzyline, a marked tachycardia occurred which they believe would have produced deleterious effects if therapy had been continued for any length of time.

8. ILIDAR· Ilidar is an adrenergic blocking agent. It is given in an oral dosage of one 25 mg tablet three times daily and is gradually increased as necessary to a recommended maximum of 300 mg daily

9 RONIACOL. It is considered a "peripheral" vasodilator like nicotinic acid and nitroglycerin. It is given by mouth in a dose of one tablet or more, or one or more teaspoonfuls of the elixir daily. The tablets contain 50 mg. of Roniacol tartrate. Roniacol with Aminophyllin provides 50 mg. of Roniacol and 100 mg. of aminophylline per tablet in a base containing magnesium trisilicate Roniacol Elixir contains 50 mg. of Roniacol per teaspoonful in a portwine flavored vehicle

10 ARLIDIN: The effective dose is given as 2.5 to 10 mg subcutaneously and 12 to 30 mg orally (37a). This drug is a derivative of the epinephrine-ephedrine type of compounds and is phenyl secondary butyl-nor suprifen Pomeranze, Gadek, Pitman and Scherl (86) administered the drug orally in doses from 3 to 12 mg three times daily to 24 diabetic patients complaining of intermittent claudication. The treatment periods lasted from 3 to 21 months Nineteen patients were considered to have been successfully treated with Arlidin

11 NITRITES. Nitroglycerin is not as useful for intermittent claudication of the lower extremities as it is for that of the coronary arteries. However, in its action in releasing vascular spasm, Foley *et al* (38, 74) have found glyceryl trinitrate to be of use as a diagnostic test of peripheral pulses When an absent or markedly diminished pulse becomes bounding after sublingual administration of nitroglycerin it can be concluded that the reduced pulsation was due to spasm of the artery under consideration Peritrate (71) has also been suggested

Surgical Therapy: 1 PARAVERTEBRAL BLOCK Paravertebral blocks have been used for prognostic and therapeutic purposes in arteriosclerosis obliterans Single blocks or continuing blocks by means of the polyethylene catheter are used. Alcohol or procaine may be used Saland and Klein (39) used paravertebral alcohol block in 13 patients with arteriosclerosis obliterans with good results in most of the cases Bonica (40) treated 33 such patients with phenol or absolute alcohol. Sixteen experienced good results, 5 obtained fair results, and in 12 there was no improvement, requiring subsequent amputation. McKittrick (41) found alcohol block to give complete relief of pain and a vasodilatation lasting 4 to 7 months.

2. LUMBAR SYMPATHECTOMY: The indications for sympathectomy in

"The routine use of lower segment femoral and popliteal arteriograms at the time of operation to supplement the preoperative arteriograms should enable the surgeon to avoid ill-fated endarterectomy where hopeless disease exists beyond his scope of surgical attack. To avoid the complication of thrombosis, the dissection should be extended beyond all the diseased intima, but the diffuse nature of arteriosclerosis often precludes such a maneuver. The number of good results following endarterectomy may be expected to increase as the principles for selection of patients for this operation are clarified. The more localized the disease, the better results may be expected to be. Thrombosis, hemorrhage and rupture are the most usual complications"

Hoye and Warren (89) reported on follow-up studies of arterial reconstruction of the iliofemoral trunk of 31 extremities in 29 patients with symptomatic arteriosclerosis obliterans. The ages varied from 32 to 73 years, with a mean age of 58 years The follow-up period was from 2 to 29 months Of 29 patients with grafts inserted, 26 left the hospital with a graft that was patent Of 16 arterial grafts, 12 closed; 10 had closed within 9 months, one at 1 year and 1, 2½ years after insertion Of 13 venous grafts, 8 were found reoccluded, 6 within 6 months, 1 at 8, and 1 at 9 months.

Anticoagulant Drugs: The problem of long term anticoagulants has been considered under acute myocardial infarction In general, if anticoagulant drugs can be given safely and easily for a long period, their use would prevent thrombosis and, therefore, would be of considerable value in arresting one important factor in the progress of arteriosclerosis obliterans However, neither heparin nor dicumarol can be given safely and simply for long periods without strict medical care. Furthermore, heparin is so expensive that its use is considerably limited and since it must be given by continuous, or frequent intravenous injections its practical use is restricted to relatively short periods, such as 1 or 2 weeks.

The real danger of sudden thrombosis of large or small extent in arteriosclerosis obliterans is one which exists for years rather than for months, therefore, the use of dicumarol is not practical at present as routine treatment Anticoagulant therapy is of definite value in cases in which a sudden arterial occlusion has occurred, both to prevent extension of the thrombosis and to prevent subsequent thrombosis in arteries distal to the point of occlusion in which acute spasm has developed Duryee recommends that heparin should be given, preferably in saline form, subcutaneously (61), every three hours in doses adequate or triple the control clotting time. When the coincidentally administered coumarin derivative (Tromexan, Dicumarol, etc.) has elevated the prothrombin time to two to two and one-half times its normal level the heparin is discontinued Initial doses of dicumarol average 300 mg. and Tromexan 1500 mg. followed by daily doses

obtained in patients with the least severe disease, over 85 per cent showing definite improvement A gratifying incidence of improvement was also achieved among more than three-fourths of the patients with impending gangrene. Even among the patients with frank gangrene, definite improvement with salvage of the extremity was secured in 35 per cent of the cases. A comparison of the results among the diabetic and non-diabetic groups revealed no essential difference except in the category of frank gangrene, in which a somewhat higher incidence of improvement was observed among the diabetic patients. There were no operative deaths in the entire series

De Takats and Evoy (45) report on a group of 57 patients with peripheral vascular sclerosis. In one group of patients, this operation resulted in a dramatic increase in walking ability; in a second group amputation was averted; in a third group intractable neuritic pain of the causalgic type was was benefited, and in a fourth group amputation could be performed at a lower level.

3. Endarterectomy for Peripheral Arteriosclerosis (25, 46-49, 50-52, 77, 80)· Claudication, rest pain and gangrene require restoration or the lumen of an obstructed artery or increase in collateral circulation for relief. Arterectomy (53) or the removal of portions of the entire thrombosed segment of the vessel has been suggested. Dos Santos (54) first described a procedure restoring arterial continuity, known as thromboendarterectomy. This procedure is made possible (49) by the existence of a pathologic cleavage plans lying within the media of the artery, usually in close approximation to the internal elastic membrane. A longitudinal incision into such a vessel is followed by the spontaneous separation of the vessel wall into two layers. The innermost layer can then be readily removed, leaving behind the smooth muscular surface of the tunica media Reconstruction of the artery is then possible by suturing the remaining media and adventitia

Arteriographic study is necessary to determine the exact location of the obstruction and the patency of the distal segment The best results are obtained (46) in arteries of the main arterial trunks especially if the obstruction is limited in length and is accompanied by patency of the distal segments of the artery. Endarterectomy is seldom technically feasible in vessels smaller than the popliteal artery

Gilfillan (49) reports on thromboendarterectomy from the service of Dr. E. J. Wylie. There were 39 aortic and iliac cases and 12 femoral. There were 6 deaths. There were 28 good results in th aortic and iliac series and 7 good results of 11 survivors in the femoral series. The major complications were due to hemorrhage, thrombosis, renal failure, cerebrovascular accidents and coronary occlusion Patients with major cardiac, cerebral or renal disease should not be considered as candidates.

Barker and Cannon (50) evaluate endarterectomy as follows

nomenon. A patient with acute popliteal arterial occlusion complains of pain in the lower portion of the leg just above the ankle. A patient with acute femoral occlusion complains of pain around the knee. The objective signs of acute arterial occlusion consist in pallor of the skin, a reduction in temperature of the skin and a loss of a previously present pulsation. The collapse of superficial veins is a concomitant. The therapy, which is emergent (75), includes slight lowering of the limb, vasodilators, anticoagulants, paravertebral block. If seen within the first 6 to 8 hours, the problem of surgical removal of embolic obstruction at the aortic bifurcation or in the femoral or iliac arteries must be considered.

Acute thrombotic occlusion occurs predominantly in the lower extremities but it can also occur in the upper extremities. Allen, Hines and Barker (5) in a review of 100 cases of sudden occlusion found 13 due to thrombosis of the upper extremities, 3 in the right and 10 in the left arm. Specifically, 2 were axillary, 8, brachial, 1, radial and 2, ulnar in origin. McLaughlin and Bradley (87) report an instance of axillary thrombosis in a diabetic woman.

PERIPHERAL ARTERIAL EMBOLISM

Haimovici (64) studied 330 cases of peripheral arterial embolism which occurred in 228 patients. In 72 patients (31.5 per cent) the source of embolism was from a mural thrombosis associated with myocardial infarction and in 44 patients (19.3 per cent) the source was arteriosclerotic heart disease with auricular fibrillation, giving a 50 8 per cent incidence of peripheral arterial embolism from an arteriosclerotic source Rheumatic heart disease, subacute bacterial endocarditis and pulmonary vein thrombosis accounted for the remainder of the emboli except for 3 1 per cent of the entire series where the source was undetermined.

The incidence of the sites of lodgment of the emboli, for the entire series, was as follows Femoral artery, 38 5 per cent, popliteal artery, 14 2 per cent; common iliac artery 13 6 per cent, bifurcation of the aorta, 9 1 per cent; brachial artery 9 1 per cent, external iliac artery, 3.0 per cent, axillary artery, 4 5 per cent, posterior tibial artery, 2 8 per cent; anterior tibial artery, 2.8 per cent; radial artery, 1.2 per cent, and ulnar artery, 1 2 per cent.

The sudden onset of pain after acute arterial occlusion occurs in a little over 50 per cent of patients (5, 64). The pain may be progressive in onset, there may be a painless occlusion, or gradually developing numbness, tingling and cold The initial site of pain is in the region of the lodgment of the embolus The chief physical findings (5) are lowered surface temperature, collapsed superficial veins, pallor and the loss or diminution of reflexes, sensation and muscular strength and absence of pulsation in some of the involved extremity in which pulsations were previously present.

Sudden peripheral arterial embolism must be differentiated from acute

of one-half to one-third of the initial dose. Daily prothrombin times should be taken.

Intermittent heparin therapy (62, 84) for periods ranging from about 1 to 16 weeks had no beneficial effects in *intermittent claudication.*

Androgens and Estrogens: Godden and Hines (85) treated six men with appropriate placebos, intramuscular injections of solutions of testosterone propionate and cyclopentylpropionate (depotestosterone) and oral doses of methyltestosterone and estrogen (premarin) During the control period and treatment with placebos and active agents each patient was walked at 120 steps per minute to determine his claudication time. The treatment did not increase the walking distance of any of these patients by 50 per cent or more It was concluded that testosterone or testosterone and estrogen as used did not cause significant improvement of intermittent claudication in patients with occlusive arterial disease due to arteriosclerosis obliterans.

The active agent for injection was 50 mg. of testosterone propionate given intramuscularly each day for 3 days. For oral treatment a tablet containing methyltestosterone, 10 mg., and estrogen (premarin), 1.25 mg. was used. The tablet was given three times daily for 3 weeks Further a 1 cc. solution of 200 mg. of cyclopentylpropionate was injected once each 2 weeks for 1 month in another trial period.

Myofascial Component of Intermittent Claudication: Travell *et al* (63, 76) found that some patients with arterial insufficiency of the lower extremities suffered pain and limitation on walking because of a superimposed or accompanying myofascial component. Patients with intermittent claudication should all be examined for the presence of trigger areas in their gastrocnemius, soleus and anterior tibial muscles and when found should be treated by procaine hydrochloride infiltration or ethyl chloride spray.

Prognosis: Patients with arteriosclerosis obliterans have a shortened expectancy of life In the Mayo Clinic Series (5), 54.6 per cent of 116 patients died within *3 years of their first visit. The majority died in a manner* suggestive of, or actually due to, coronary occlusion. The presence of diabetes *further shortened the life expectancy*

ACUTE ARTERIAL OCCLUSION

Acute arterial occlusion occurs in atherosclerosis for two reasons: 1) thrombosis of an atherosclerotic vessel of the lower extremity, or 2) an embolus from a mural thrombus in the left ventricle While the patient with slowly progressive atherosclerosis of the peripheral arteries complains of calf claudication on walking, the onset of pain in acute arterial occlusion is sudden and severe. Some patients may complain of progressive intermittent claudication over a period of days or weeks as a pre-occlusive phe-

(65) that aneurysms of the superficial femoral arteries are about ten times more frequent than those of the deep femoral arteries and about four times less common than those of the popliteal arteries.

Diagnosis is made by palpation of the expansile pulsating mass, by auscultating a systolic bruit, and by the presence of roentgen evidence of calcification of the aneurysmal sac The aneurysms may be symptomless or may give rise to pain on rupture, if the aneurysm enlarges rapidly or if it presses on a nerve. Thrombosis frequently develops in arteriosclerotic aneurysms of the lower extremities (5) and may suddenly occlude the artery distal to the aneurysm by extension of thrombosis or by embolism

Bilateral femoral arterial aneurysms are rare. Rogers and Rinzler (65a) reported one case and found only one other reported case due to arteriosclerosis Arteriosclerotic aneurysms of the popliteal artery are commonly bilateral. Aneurysms of the subclavian, axillary and brachial arteries are less common than those of the lower extremities

Treatment of peripheral aneurysms of arteriosclerotic origin is unnecessary in most cases. Ligation of the arteries proximal to the aneurysm has been advocated. Obliterative endoaneurysmorrhaphy is also suggested

Aneurysmorrhaphy consists of infolding and obliteration of the aneurysmal sac (66). The Matas technic consists of opening the sac widely, and the sac, with its afferent and efferent arteries is as fully exposed as possible and the entering vessels especially are so well isolated that a piece of rubber tubing can be passed under it. The same thing can be done with the efferent vessels With circular stitches, the efferent and afferent orifices are closed from within by a series of similar circular stitches, placed at short intervals from one end of the sac to the other, the whole of a small aneurysm can then perhaps be obliterated, but if the sac is larger and friable, so that the stitches will not hold, the wall of the aneurysm is better infolded and made into a compact mass by mattress stitches The restorative endoaneurysmorrhaphy is possible when the original arterial lumen is well preserved. The operation permits the current to resume its natural course

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arterial thrombosis due to arteriosclerosis obliterans. The differential diagnosis must essentially rely upon the presence or absence of a source of emboli. This differential is especially important when an embolectomy is contemplated. Localization of the embolus is determined by: (1) knowledge that emboli lodge usually at bifurcations, (2) palpation of pulsation for the site of occlusion is distal to the point of normal pulsations; (3) history of the site of the initial pain, (4) the oscillometric readings, and (5) arteriography

Prognosis: This is related to the survival of the extremity and the survival of the patient In 1935, the outcome in 100 cases of sudden arterial occlusion was as follows (5). (1) of 46 cases of embolism involving 57 extremities, gangrene occurred in 26 extremities (12 amputations with 5 postoperative deaths, 12 deaths without amputation), recovery occurred in 31 extremities (death without gangrene in 3 cases); (2) of the 54 cases of thrombosis, involving 60 extremities, gangrene occurred in 31 extremities (15 amputations with postoperative deaths, 14 deaths without amputation), recovery occurred in 29 extremities with 1 death without gangrene

Haimovici (64) found 34 9 per cent gangrene in the lower extremities *and 7.8 in the upper extremities after peripheral arterial emboli. Hospital* mortality was about 50 0 per cent The prognosis as to survival of the extremity depended essentially upon his heart condition and the possibility of further embolism to vital viscera

Treatment: Treatment consists of the use of the following modalities alone or in combination as previously considered under arteriosclerosis obliterans.

1. Vasodilator drugs
2. Interruption of sympathetic pathways.
3. Anticoagulants
4. Physiotherapeutic measures.
5. Embolectomy.
6. Arterectomy.
7. Sympathectomy.
8. Amputation.

PERIPHERAL ARTERIAL ARTERIOSCLEROTIC ANEURYSMS

The usual *cause of aneurysms of the lower extremities is arteriosclerosis,* it is practically the only cause in those more than 60 years of age (5) The usual sites of aneurysms of the lower extremities are the popliteal space and Scarpa's triangle. This is believed to be due to less muscle protection in these regions and to the fact that the frequent bending to which these sites are subjected may tend further to weaken a diseased intima and cause medical degeneration with subsequent aneurysmal formation. Matas states

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CHAPTER XII

Retinal Aspects of Arteriosclerosis

BLOOD SUPPLY

THE OPHTHALMIC artery arises from the internal carotid immediately below the anterior clinoid process. It enters the skull through the optic foramen. It has seven branches which includes the central retinal artery (Plate XI). This comes off the ophthalmic artery close to the optic foramen, perforates the optic nerve about 6 mm. behind the globe. After reaching the optic papilla, it divides into an upper and lower branch, each of which divides again into nasal and temporal branches. The veins of the retina accompany the corresponding arteries. They unite in a central vein and empty into the superior ophthalmic vein (1).

Retinal Arteriosclerosis: Intimal atherosclerosis (1-10) is found in the central retinal artery and early portion of the retinal branches The point of predilection of atherosclerosis in the retinal artery (Fig 11) is found as the artery pierces the dural sheath and passes in the nerve to the crural sheath (11). Plaques are less frequent in the remainder of the arterial tree but are found even in the arteriolar portions. Thrombi may form at the site of these atheromata and result in central retinal artery and vein thrombosis (Figs 53 and 54).

OPHTHALMOSCOPIC SIGNS OF ARTERIOSCLEROSIS

1. **Localized Constrictions in the Arteries (beading):** These constrictions in the arteries correspond to localized regions of endothelial proliferation They are minute atheromatous plaques in the vessel wall (Fig 55) Because changes occur especially in the central retinal artery in its course through the optic nerve, lesions visible through the ophthalmoscope may be assumed to be merely the fringes, the major portion being obscured from view

2. **Variations in Caliber:** The retinal arteries are often excessively narrow and may, in addition, be straight, branching at acute angles (5, 10) When the retinal vascular lumen intra-neurally is partially occluded, the caliber of the ophthalmoscopically visible retinal vessels is narrowed

3. **Arteriovenous Constriction (Gunn's sign):** Thickening of the arterial wall can encroach upon the limited space within the arteriovenous adventitia and can reduce the venous channel (11, 12). This is Gunn's sign and the arteriovenous constriction is due to a change in the tortuosity of the artery which produces a slight shift in its position will drag the vein at

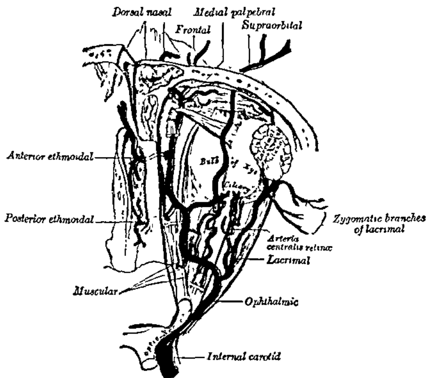


Plate XI. The ophthalmic artery and its branches. (From *Gray's Anatomy*, 26th Ed., 1954 Courtesy Lea & Febiger, Philadelphia.)

the point of crossing a little to one side (10). This sclerotic etiology of venous constriction is to be distinguished from venous engorgement with increased tortuosity of the veins which may also produce the appearance of arteriovenous displacement. This is found in conditions with no vascular disease, therefore, arteriovenous constriction is a good sign of, but not necessarily a pathognomic sign of vascular disease

4. **Tortuosity of the Retinal Vessels:** In the early stages of retinal arteriosclerosis, when the disease has as yet involved only the smallest vessels, extreme dilatation and tortuosity of the larger branches may be observed.

5. **Copper Wire and Silver Wire Arteries:** Normally the retinal arterioles appear a clear pink, and a small central reflex of light appears along the wall (9). This light streak is formed by the reflection of the light from the convex cylindrical surfaces of the blood column, and the surrounding vessel walls, which are relatively transparent The light streak in the arteries is always wider and brighter than that of veins of similar caliber. The outer streak of the muscle coat (6) must therefore contribute an important factor to the light stripe, and, similarly, any changes in the thickness of the coat of the wall of the vessel with an associated increase in its refractive index



Fig 53 An ophthalmoscopic picture of the retina demonstrating occlusion of the central retinal artery. Note the cherry-red spot at the macula and the presence of trucking (Courtesy of Dr. Dan M Gordon, New York Hospital)



Fig 54 An ophthalmoscopic picture of the retina showing an occlusion of a branch of the central retinal vein (Courtesy of Dr Dan M Gordon, New York Hospital)

should cause an increase in the width and brightness of the arterial light streak

As the light streak increases in width, it eventually becomes so broad that it occupies most of the surface of the vessel. The vessel then has the appearance of burnished copper (2)—"copper wire."

When the arteriolar sclerosis is extreme, the vessel wall is so thickened as a result of hyalinization and lipid infiltration, that the vessel wall obscures the blood column. The artery then appears as a white cord, even though blood is still circulating through it. This is a "silver wire" appearance.

6. Hemorrhages and Exudates: Serous transudates in the retina (*11, 13*) occur frequently in arteriosclerosis as well as in many other conditions, and may appear either with or without retinal hemorrhages. The exudates are white areas which are sharply delimited and shiny (13), with a white to yellowish appearance. When the exudates are less neatly delimited, they appear soft or cotton wool, a finding more usually seen in hypertensive retinopathy. Accompanying the white spots are the red areas of fresh hemorrhage which may occur at various levels of the retina, may assume many shapes and may be single or multiple.

RETINAL ARTERIOSCLEROSIS WITH AND WITHOUT HYPERTENSION

The outstanding features in retinal arteriosclerosis with hypertension are reduction in caliber of the whole arterial tree with disappearance of the reflex stripe and arteriovenous compression There is thrombosis of large branches, scattered hemorrhages and exudates In retinal arteriosclerosis without hypertension, the larger vessels are of normal calibre and the arterioles are normal. There is beading of the larger vessels, irregularity in the light streak, visible wall and arteriovenous compression. Atheromata at the lamina cribrosa are invisible (6) and by ophthalmoscope one sees: (a) narrowing of the arterial tree, and (b) increased number of branches at the disk border. Lesions at or near the disk cause: (a) localized irregularity of the blood column, and (b) a white or opaque area in the wall of the vessel.

Choroidal sclerosis produces degenerative changes in the intervascular stroma and pigment epithelium. The nerve may be irregularly shaped deposits of pigment in the retina or choroidal patches which have a mottled appearance (6, 14-16).



Fig 55. An ophthalmoscopic picture of the retina with the arrow pointing to an atheroma of the superior temporal artery as indicated by indentation of the arterial wall (Courtesy of Dr Dan M Gordon, New York Hospital)

CIRCULATORY DISTURBANCES OF THE RETINA

There are two very important disturbances to the blood supply of the retina; namely, thrombosis of the central vein which produces maximum stasis and hyperemia, and occlusion of the central artery which causes maximal anemia (10, 17). The first type occurs more commonly than the second, but both may result in sudden and severe visual disturbances.

Thrombosis of the central vein usually occurs quite suddenly A little vision may be retained, such as finger counting or perception of hand movements at short distances, but occasionally the vision is almost completely lost. The vision may deteriorate within a few days. In this case the ophthalmoscopic picture becomes progressively worse and the hemorrhages in the retina become more numerous and massive. Secondary glaucoma is a disturbing complication.

Thrombosis of the central vein ophthalmoscopically shows the many enormous hemorrhages which are spread profusely all over the fundus. The disc borders are blurred The veins are tremendously dilated. The arteries are narrow and partially invisible. Hemorrhages, superficially located and flame-shaped; those more deeply situated are round and irregular. The hemorrhage may extend into the vitreous. As time goes on, exudates may be seen.

Thrombosis of a branch of the central vein occurs more often than that of the central vein itself, and the superior temporal vein is most commonly affected.

Thrombosis of the central vein is almost always unilateral. The afflicted patients usually belong to the middle and upper age groups and often suffer from generalized vascular disease.

In occlusion of the central artery (Fig. 53), the visual loss occurs quite suddenly (10, 17-19). The patient sees a gray fog or occasionally a colored one, which rapidly becomes denser and results in blindness of the eye Frequently, the patient is aware of his disease for the first time upon awaking in the morning when he becomes immediately conscious of blindness in the affected eye. The ophthalmoscope reveals a very pale disk and threadlike arteries which appear as thin red lines The light reflex is thin or absent. At the posterior pole the fovea centralis is almost always replaced by a cherry-red spot The whitish coloration of the retina appears several hours following the sudden blindness, but it disappears after some time, so that after four weeks the fundus may again show its normal color (17). Closure of branches of the central artery occurs more frequently and one may observe a whitish coloration of the fundus only in the region around one vessel

If occlusion of an isolated branch occurs, there is a special thinning of the affected vessel branches after some time. The disk then becomes pale

in the corresponding quadrant only. The papilla may remain unaffected by the occlusion of smaller branches.

Karpe (20) and Henkes (21-24) indicate that these are changes in the electroretinogram that may be diagnostic and prognostic in central retinal artery and central retinal vein occlusion.

ANTICOAGULANTS FOR OCCLUSIVE VASCULAR DISEASE OF THE RETINA (15, 25-60)

In 1951, Duff, Falls and Linman (34) summarized the world literature of treatment of thrombosis of the retinal veins with the anticoagulant drugs, heparin and dicumarol. Of 109 patients with thrombosis of the retinal vein who were treated with heparin, the condition of 59 per cent appears to have improved; that of 15 per cent was unchanged, and that of 27 per cent had grown worse, *12 per cent had glaucoma, and 6 per cent of the eyes* required enucleation. For those who improved, the average initial visual acuity was 0.251 and the final vision was 0.60 Of 84 patients with thrombosis of a tributary retinal vein treated with heparin, the condition of 59 per cent had improved, that of 24 per cent was unchanged, that of 17 per cent had grown worse, only 2.3 per cent had glaucoma, while only one eye required enucleation. For patients who showed improvement, the initial visual acuity averaged 0 33, and the final vision was 0 68.

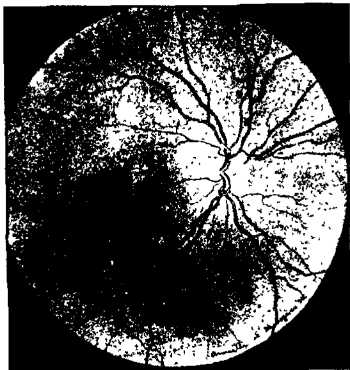
Of 23 patients with thrombosis of the central retinal vein treated with dicumarol, the condition of 70 per cent appears to have improved, that of 26 per cent was unchanged That of only one had grown worse, none of the eyes became glaucomatous or required enucleation For 10 patients who improved, the visual acuity was 0 33 before, and 0 76 after treatment. Eight of the 11 patients with thrombosis of the tributary retinal veins showed improvement when treated with dicumarol, while the condition of 3 became worse For 6 of the patients who showed improvement, the initial vision averaged 0.18 while it was 0 68 after treatment.

Duff, Falls and Linman (34) reviewed 140 untreated patients, or a total of 148 eyes The average visual acuity for all eyes at the time of the first examination was 0 08 Secondary glaucoma developed or was present at the time of the initial observation in 38 patients. Enucleation was necessary in 18 eyes A follow-up of these patients, permitting an observation period of from 3 months to 20 years was carried out Of 70 patients with complete occlusion, the condition of 49 per cent appeared to have grown worse and secondary glaucoma developed in 43 per cent In 35 per cent, the condition was unchanged, in only 15 per cent had it improved The final average visual acuity (0 079 was slightly less than that observed at the initial examination (0 088). Of 11 patients with incomplete occlusion in a 1 to 12-year observation period, only 1 became worse, and in none had secondary glau-



Fig 56 Flat preparations of human diabetic retinas stained with periodic acid fuchsin *(Above)* Single discrete thick-walled capillary aneurysm. *(Below)* Cluster of capillary aneurysms (Courtesy of Dr. Bernard Becker and *Annals of Internal Medicine*)

coma developed. In 54 per cent the condition was unchanged, whereas in 36 per cent it had improved. In this group the final average visual acuity (0 546) was actually somewhat improved over that observed initially (0 420). Follow-up observation of 71 patients with thrombosis of the retinal tributary veins in the 6 to 20 year observation period revealed a change in the visual acuity from 0.319 to 0 388. The condition of 42 per cent of these patients appeared to have improved, that of 27 per cent was unchanged,



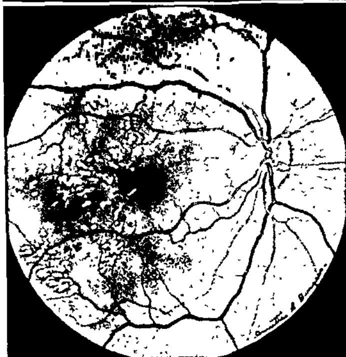


Fig. 57. Drawings of the ophthalmoscopic picture of diabetic retinopathy. *(Above)* Early diabetic retinopathy with few scattered aneurysms and hemorrhages. *(Below)* Later stage with aneurysms surrounded by hemorrhages and exudates. (Courtesy of Dr. Bernard Becker and *Annals of Internal Medicine*.)



FIG 56 Flat preparations of human diabetic retinas stained with periodic acid fuchsin *(Above)* Single discrete thick-walled capillary aneurysm *(Below)* Cluster of capillary aneurysms. (Courtesy of Dr Bernard Becker and *Annals of Internal Medicine*)

coma developed In 54 per cent the condition was unchanged, whereas in 36 per cent it had improved. In this group the final average visual acuity (0.546) was actually somewhat improved over that observed initially (0.420). Follow-up observation of 71 patients with thrombosis of the retinal tributary veins in the 6 to 20 year observation period revealed a change in the visual acuity from 0.319 to 0.388. The condition of 42 per cent of these patients appeared to have improved, that of 27 per cent was unchanged,

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while that of 31 per cent had grown worse. Secondary glaucoma had developed in 7 per cent; enucleation was required in 6 per cent.

This indicates that the prognosis for adequate visual acuity following untreated thrombosis of a tributary or central vein is discouraging while the collected experience with anticoagulant therapy indicates that the prognosis for visual improvement is favorably influenced.

Heparin was administered by intermittent injections or by continuous infusion for an average of 6.7 days (34). Dicumarol was given for an average of three months Institution of treatment must be prompt particularly after thrombosis or occlusion of a retinal artery if the results are to be favorable

STELLATE GANGLION BLOCKS

Reports on the efficacy of stellate block in occlusive disease are mixed. Grelaut (61) reported 3 cases of central retinal artery embolism and 1 case of thrombosis of the central retinal vein which were markedly improved by block. Caston (62) was able to restore vision 15 minutes after a stellate ganglion block in a patient with central retinal artery occlusion, even though the block was attempted 8½ hours after loss of vision. Bonica (63) found the procedure uneffective in three patients.

DIABETIC RETINOPATHY

This retinal picture is a specific one and may exist with or without atherosclerosis or arteriosclerotic lesions Diabetic retinopathy (30, 64-68) is identified pathologically by a characteristic pattern of numerous aneurysms with surrounding hemorrhages and exudates (Fig. 56). These latter are explained in part by leakage of proteins and red cells through the walls of the aneurysms There is a great statistical correlation between the occurrence of diabetic retinopathy and the Kimmelstiel-Wilson lesion in the kidneys of the same diabetic patients, as found at autopsy

By ophthalmoscope, the earliest changes seen are usually punctate microaneurysms of capillaries, singly and in clusters, in and about the macula (Fig. 57). These tend to occur in crops, becoming more numerous and surrounded by small exudates and hemorrhages. Hemorrhages into the vitreous are followed by organization and vascular ingrowth, known as retinitis proliferans.

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CHAPTER XIII

Renal Aspects of Arteriosclerosis

BLOOD SUPPLY

THE RENAL arteries come off the abdominal aorta on a level with the first lumbar vertebra (Plate VIII). As the artery enters the hilus, it usually divides into three main stems, one of which passes toward the upper part of the pelvis, a second to its middle portion, and a third to its lower. Each of these primary stems then divides so that 7 to 9 secondary branches result, these branches are distributed anteriorly and posteriorly

DIABETIC GLOMERULOSCLEROSIS

In 1936, Kimmelstiel and Wilson (1) described a clinical syndrome, now known as diabetic glomerulosclerosis, in which at an autopsy they found a peculiar focal hyalin thickening of the intercapillary connective of the glomerulus, associated with considerable renal arteriolo- and arteriosclerosis. In the evolvement of the full picture of diabetic glomerulosclerosis, the patient may pass through the various degenerative changes of diabetes and thus diabetic and arteriosclerotic coronary artery disease may precede the onset of the renal lesion. Most observers have stressed the relationship between intercapillary glomerulosclerosis and renal vascular disease (2, 3). The possibility exists that there may be a special predilection for sclerosis of the efferent arterioles with the resultant increase in intraglomerular pressure serving as an aggravating factor in the production of the intercapillary hyalin deposits.

The clinical syndrome consists of retinopathy, proteinuria, hypertension, nephrotic and or cardiac edema, and progressive azotemia in a patient whose diabetes is either mild or severe. Rifkin, Lester and Berkman have listed the following clinical variants of the disease (2, 3):

1. Diabetes mellitus, hypertensive disease, edema, proteinuria and retinopathy.
2. Mild diabetes mellitus, retinopathy, peripheral vascular disease, and proteinuria with or without hypertension or renal insufficiency
3. Diabetes mellitus, arteriosclerotic heart disease, congestive failure, proteinuria and retinopathy.
4. Diabetes mellitus, hypertensive disease with or without cardiac failure, and proteinuria.
5. Renal insufficiency and/or edema of undetermined etiology in a latent diabetic patient with some other major illness

6. Nephrotic syndrome in a juvenile diabetic with retinopathy or without hypertension or renal impairment in early stages.

7. Diabetes mellitus, proteinuria, retinopathy, and peripheral neuropathy.

The findings of diabetic retinopathy have been described in Chapter XII. Diabetes is present at least eight years before the onset of the renal lesion (4). The prognosis is poor with an average duration of life after the onset of the syndrome 6 to 7 years with a range of 2 to 13 years. Uremia, myocardial infarction, and acute cardiac failure are the most frequent causes of death

The complete nephrotic syndrome inclues marked albuminuria, hypoprotimineuria, hypercholesterolemia and edema. In the syndrome, albuminuria may vary in degree, edema may not be present even though the rest of the clinical picture exists. *A prominent urinary finding is the presence* of doubly refractile lipoid droplets in epithelial cells or casts With polarized light they present a typical and easily recognizable appearance of maltese crosses. This serves to distinguish the albuminuria of congestive failure with edema. It is chiefly found in fresh acid urine and the urine may have to be examined daily to find them, since the amount of anisotropic material varies from day to day The plasma proteins show a low serum albumin, an elevated alpha-2 and beta globulin, and normal gamma globulin. The urinary proteins consist chiefly of albumin and alpha-1 globulin with no increase in the beta and gamma globulin

Renal function studies reveal a reduction in glomerular filtration rate, renal plasma flow, maximum tubular excretory function.

Treatment: The patient is given a diabetic diet with about 100 gm. of protein daily and 150 to 200 gm. of carbohydrate. The salt content of the diet should be less than 2 gm. per day in the presenco of edema In the patient with poor renal function, the protein in the diet should be reduced to 30 to 50 gm. daily, but the calories must be adequate in other respects to prevent malnutrition. The fluid volume is regulated so that a daily urine volume of 1,200 to 1,500 cc. is produced.

Digitalis and mercurial diuretics are given in the presence of heart failure. The problem of poor renal function must always be borne in mind.

RENAL ARTERY SCLEROSIS AND THROMBOSIS

Arteriosclerotic renal disease, even in the presence of normotension, may produce proteinuria, granular and hyalin casts, and red and white blood cells This may be regarded as a static, local atherosclerotic lesion and need not of itself lead to hypertension. Fishberg (15) believes that the arteriosclerotic kidney is for the most part of little clinical significance. However, progressive sclerosis of the renal artery with gradual occlusion of the lumen is a natural counterpart of the Goldblatt experiment of narrowing the renal

arteries with silver clamps. Reports of the sudden production of essential hypertension by unilateral or bilateral thrombosis of the renal arteries have been published (5-14).

Perera and Haelig (6) state that hypertension associated with unilateral renal disease is of an acute, severe, and rapidly progressive type. The sudden appearance of a striking diastolic blood pressure after the age of 50 years, in a person known previously to have been normotensive, should lead to suspicion of unilateral renal disease There is also a high frequency of headaches, convulsions and advanced retinopathy in almost all but young children. The clinical picture is that of the accelerated or so-called "malignant" type of hypertension.

The pathogenesis might occur as follows (10): The circulatory impoverishment due to renal artery sclerosis causes gradual atrophic changes in the renal parenchyma Concomitantly, sufficient pressor substance is elaborated by the ischemic tissue to maintain and sustain a severe hypertension Hussar and Bornstein (5) describe an instance of a man aged 55 who had preexisting arteriosclerosis of both kidneys. A severe gastrointestinal hemorrhage from an arteriosclerotic blood vessel in a penetrating duodenal ulcer threw the patient into shock Thrombus formation took place in both renal arteries following this episode Hypertension then ensued and the patient died of renal insufficiency. The arteriosclerotic lesions were confirmed at autopsy

Wolffe and Donnelly (11, 12) reported their experience with eleven cases of acute renal artery thrombosis The attacks were ushered in with severe pain over the kidney region or in the loin and resembled renal colic The symptoms included frontal headache, backache and generalized abdominal pain The onset in one patient mimicked coronary thrombosis because of the localization of the pain to the chest Most patients show an elevated blood pressure, frank hematuria, and elevation in temperature *Intravenous urography revealed filling defects on the affected side* All were treated medically. However, when confronted with a severe, sudden, unexplained hypertension, obstruction to the blood supply to the kidney should be seriously considered among the possible causes, especially since nephrectomy in unilateral renal disease is curative. Thromboendarterectomy as an alternative method of treatment to nephrectomy was offered by Freeman and his co-workers (14). A 46-year-old white male with almost complete occlusion of the left renal artery, demonstrated pre-operatively by aortogram and proved at operation, was treated by blunt curettage of the obstructive thrombus. An aortogram, done 2 years after thromboendarterectomy, showed good filling of the left renal artery with a persistent reduction of the pre-operative hypertension.

Poutasse and Dustan (16) found 8 patients with severe hypertensive

vascular disease who were shown by aortography to have arterial filling defects of the renal artery due to arteriosclerotic plaques at the aortic orifices or within the renal artery. Two of these patients, men aged 33 and 49 years had prompt remission of the syndrome of malignant hypertension following nephrectomy. Three other elderly patients who underwent nephrectomy had less striking results. The blood pressure in these three returned to the pre-malignant level rather than to normal levels. Of the remaining 3 patients, 2 died of their disease without surgery (which was contraindicated) and 1 is on medical treatment.

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The clinical picture has two phases: (1) those of respiratory insufficiency and (2) those of cardiac insufficiency manifested by right heart failure. The incidence symptoms and signs in 25 cases reviewed by Parmley and Jones (1) are as follows:

1	Dyspnea	25 cases	(100%)
2	Cyanosis	25 cases	(100%)
3	Cardiomegaly	21 cases	(84%)
4	Peripheral edema	20 cases	(80%)
5.	*Hepatomegaly*	13 cases	(50%)
6.	Precordial pain	11 cases	(44%)
7.	Orthopnea	7 cases	(28%)
8	Hemoptysis	7 cases	(28%)
9.	Somnolence	3 cases	(12%)
10	Clubbing	2 cases	(8%)

Dyspnea, cough, hemoptysis and cyanosis are the initial symptoms. While, at first, dyspnea occurs only on exertion, as the disease progresses, it is also evident at rest. It is to be noted that although dyspnea and cyanosis are constant, that orthopnea may not accompany these symptoms. Sputum may be moderately abundant and mucoid to mucopurulent Hemoptysis may occur. Eventually the respiratory insufficiency is complicated by cardiac insufficiency with signs mainly of right heart failure, hepatomegaly, ascites and peripheral edema. Exertional syncope and exertional chest pain, resembling angina, may also be present.

Positive physical findings are limited to the heart and organs affected later by an elevated venous pressure. Examination of the heart reveals increased retrosternal dullness, widening of the conus area and distinct pulsating bulge of the precordium, most marked along the left margin of the sternum These findings are characteristic of right ventricular hypertrophy. Systolic murmurs may be present over the precordium due to relative tricuspid insufficiency, and over the pulmonic area due to dilated pulmonary artery. Diastolic murmurs at the pulmonic area and left sternal border may be present because of a functional pulmonary valvular insufficiency. Various degrees of cyanosis are seen. Clubbing of the fingers and toes, though encountered, is not common

Because of the right ventricular failure, the lung fields remain relatively clear of rales. This has been used as a paramount diagnostic point. However, hydrothorax may occur despite the absence of pulmonary rales.

Routine laboratory studies are normal except for a compensatory polycythemia. Hemodynamic studies at rest utilizing the technique of right heart catheterization shows the following (2)· 1)markedly elevated pulmonary artery pressure, 2) normal systemic artery pressure, 3) low cardiac

CHAPTER XIV

Pulmonary Aspects of Arteriosclerosis

BLOOD SUPPLY

THE MAIN pulmonary artery arises from the right ventricle and after coursing anterior to the aorta for a few centimeters, it divides into right and left branches to supply the respective lungs. The right branch proceeds posterior to the arch of the aorta and the left anterior to the descending aorta. The branches sub-divide to supply each lobe of the lung.

CLINICAL ASPECTS

Arteriosclerosis of the pulmonary arteries may be primary or secondary in origin.

Primary pulmonary arteriosclerosis is defined as a rare, progressive, fatal disease of unknown causation, characterized by an extensive narrowing of the *pulmonary arterioles by an arteriosclerotic process. The incidence is* very low. Various reports indicate that it occurs in 1:3800 autopsies, 1:12,000 autopsies, 1:1860 autopsies and 2 in 5,991 autopsies. The etiology of primary pulmonary arteriosclerosis remains in doubt. Although hypertension has been given as an important etiologic factor, instances occur without hypertension. Parmley and Jones (1) postulate that pulmonary arteriosclerosis may result from hypoxia and that the usual cause of this hypoxia is a pulmonary hypertension. In the case of primary pulmonary arteriosclerosis, an essential hypertension confined to the pulmonary circuit *may be responsible for the arteriolar lesions. Once the processes of hyper-*tension and pulmonary arteriosclerosis become manifest, a vicious circle is established, one process serving to perpetuate and increase the other.

Dresdale, Michtom and Schultz (2) have measured the pulmonary vascular pressure in this "primary pulmonary hypertension." They indicate that it can be distinguished from secondary pulmonary hypertension by the absence of any intrinsic heart or lung disease and by the absence of mechanical blocks in the pulmonary vascular bed seeded from without, e.g., pulmonary emboli.

The pulmonary vascular changes which accompany prolonged pulmonary hypertension are unlike the vascular changes seen in systemic hypertension (3-7). The predominant changes are atheromatous lesions of the stem and large elastic arteries, alone, or in combination with fibrous intimal thickening and narrowing, or obliteration of the smaller arteries. Thrombotic lesions *in various stages of organization have been seen* in the precapillary and postcapillary vessels of microscopic sizes.

The clinical picture has two phases: (1) those of respiratory insufficiency and (2) those of cardiac insufficiency manifested by right heart failure. The incidence symptoms and signs in 25 cases reviewed by Parmley and Jones (1) are as follows:

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Because of the right ventricular failure, the lung fields remain relatively clear of rales. This has been used as a paramount diagnostic point However, hydrothorax may occur despite the absence of pulmonary rales

Routine laboratory studies are normal except for a compensatory polycythemia Hemodynamic studies at rest utilizing the technique of right heart catheterization shows the following (2)' 1) markedly elevated pulmonary artery pressure, 2) normal systemic artery pressure, 3) low cardiac

output, 4) increased arteriovenous oxygen difference; 5) elevated right ventricular end-diastolic pressure, sometimes present before clinical signs of right heart failure, and 6) normal arterial oxygen saturation.

By x-ray examination, the earliest sign of this disease is an accentuated pulmonary conus-artery segment. Later, right ventricular hypertrophy may develop. Pericardial effusion may be the predominant finding at the end stage of the disease. The electrocardiogram is one of right ventricular hypertrophy

Dresdale (2) has advocated the use of priscoline in patients with primary pulmonary hypertension This sympatholytic and adrenolytic agent was able to lower the pulmonary artery pressure. The patient given priscoline in a dose of 75 mg intravenously, was able to increase his work capacity from 16 step-ups on a platform to 70 step-ups, the latter without symptoms

Primary pulmonary arteriosclerosis must be differentiated from secondary forms which may follow certain congenital heart lesions, emphysema, multiple pulmonary emboli or thrombi, mitral stenosis, kyphoscoliosis and scleroderma.

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Chapter XV

Conclusion

THE INTENT of this book has been to put under one cover the problems facing the psysician in relation to the clinical aspects of arteriosclerosis An attempt has been made to include the newer biochemical, medical, surgical, diagnostic and therapeutic knowledge in a "head to toe" approach to clinical arteriosclerosis. To carry out the intent, I have read, re-read, quoted and digested the writings of innumerable authorities and have integrated these ideas with my own clinical experience

Our treatment of atherosclerosis is still more concerned with the complications of the disease, than with the disease itself. We dilate vessels, we resect vessels, we divert vessels, we thin blood Drug and dietotherapy proposed for lowering the serum cholesterol level or altering the serum beta-lipoprotein concentration as a method for treatment of clinical atherosclerosis has included the low cholesterol-low fat diet, heparin, sitosterol, nicotinic acid (1, 2), thyroid, and lipotropic agents These therapeutic proposals have not met with uniform acceptance The following results have been reported in patients whose treatment began after their first myocardial infarction Morrison (3), after a follow up of 8 years on a low cholesterol-low fat diet, reports that of 50 control patients, 38 (76 per cent) have died of cardiovascular disease, while of 50 treated patients, 22 (44 per cent) have died. Engelberg (4) treated 105 patients with 200 mg of concentrated aqueous heparin given subcutaneously twice weekly for an average of 19 7 months, four deaths occurred in this group Twenty-one deaths occurred in a comparable control group of 117 patients who were given placebo therapy for an average of 18 7 months. Stamler, Pick and Katz (5), in their second interim report on the use of estrogen (10 mg of Premarin daily), indicate that as of May 1, 1956 (see page 36) there were 3 deaths of 49 control patients and 1 death of 53 treated patients

The apparent reversibility of the atherosclerotic process in the experimental animal has given rise to much hope for a possible application to human atherosclerosis, and, what is more, to a renewed stimulus for basic and clinical research in this field Until that glorious day when a thoroughly proved method for preventing and treating atherosclerosis is at hand, I trust that this text may serve as an aid in the diagnosis and treatment of atherosclerosis within the range of our present knowledge.

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This Book

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ARTERIOSCLEROSIS

By

SEYMOUR H. RINZLER, M.D., F.A.C.P.

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